

## P/ENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 20 July 2000 (20.07.00)	in its capacity as elected Office
International application No. PCT/GB99/03666	Applicant's or agent's file reference 44.67810/003
International filing date (day/month/year) 05 November 1999 (05.11.99)	Priority date (day/month/year) 13 November 1998 (13.11.98)
Applicant PIENE, Jan, Yngvar et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:  
09 June 2000 (09.06.00)

in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia RANAIVOJAONA Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU													
To:													
COCKBAIN, Julian Frank B. Dehn & Co. 179 Queen Victoria Street London EC4V 4EL ROYAUME-UNI													
Date of mailing (day/month/year) 21 December 2000 (21.12.00)													
Applicant's or agent's file reference 44.67810/003	IMPORTANT NOTIFICATION												
International application No. PCT/GB99/03666	International filing date (day/month/year) 05 November 1999 (05.11.99)												
<p>1. The following indications appeared on record concerning:</p> <p><input checked="" type="checkbox"/> the applicant   <input type="checkbox"/> the inventor   <input type="checkbox"/> the agent   <input type="checkbox"/> the common representative</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Name and Address NYCOMED PHARMA AS Sandakerveien 100C N-0401 Oslo Norway</td> <td style="width: 25%;">State of Nationality NO</td> <td style="width: 25%;">State of Residence NO</td> </tr> <tr> <td>Telephone No.</td> <td colspan="2"></td> </tr> <tr> <td>Facsimile No.</td> <td colspan="2"></td> </tr> <tr> <td>Teleprinter No.</td> <td colspan="2"></td> </tr> </table>		Name and Address NYCOMED PHARMA AS Sandakerveien 100C N-0401 Oslo Norway	State of Nationality NO	State of Residence NO	Telephone No.			Facsimile No.			Teleprinter No.		
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Telephone No.													
Facsimile No.													
Teleprinter No.													
<p>2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:</p> <p><input type="checkbox"/> the person   <input type="checkbox"/> the name   <input checked="" type="checkbox"/> the address   <input type="checkbox"/> the nationality   <input type="checkbox"/> the residence</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Name and Address NYCOMED PHARMA AS Drammensveien 852 N-1385 Asker Norway</td> <td style="width: 25%;">State of Nationality NO</td> <td style="width: 25%;">State of Residence NO</td> </tr> <tr> <td>Telephone No.</td> <td colspan="2"></td> </tr> <tr> <td>Facsimile No.</td> <td colspan="2"></td> </tr> <tr> <td>Teleprinter No.</td> <td colspan="2"></td> </tr> </table>		Name and Address NYCOMED PHARMA AS Drammensveien 852 N-1385 Asker Norway	State of Nationality NO	State of Residence NO	Telephone No.			Facsimile No.			Teleprinter No.		
Name and Address NYCOMED PHARMA AS Drammensveien 852 N-1385 Asker Norway	State of Nationality NO	State of Residence NO											
Telephone No.													
Facsimile No.													
Teleprinter No.													
<p>3. Further observations, if necessary:</p>													
<p>4. A copy of this notification has been sent to:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;"><input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority</td> <td style="width: 50%;"><input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:</td> </tr> </table>		<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:										
<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:												
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Christine Carrié Telephone No.: (41-22) 338.83.38												

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 21 December 2000 (21.12.00)	From the INTERNATIONAL BUREAU To:  COCKBAIN, Julian Frank B. Dehn & Co. 179 Queen Victoria Street London EC4V 4EL ROYAUME-UNI
Applicant's or agent's file reference 44.67810/003	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/GB99/03666	International filing date (day/month/year) 05 November 1999 (05.11.99)

## 1. The following indications appeared on record concerning:

the applicant  the inventor  the agent  the common representative

Name and Address PIENE, Jan, Yngvar Nycomed Pharma AS Sandakerveien 100C N-0401 Oslo Norway	State of Nationality NO	State of Residence NO
Telephone No.		
Facsimile No.		
Teleprinter No.		

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

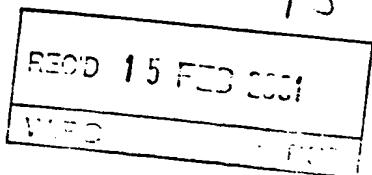
the person  the name  the address  the nationality  the residence

Name and Address PIENE, Jan, Yngvar Nycomed Pharma AS Drammensveien 852 N-1385 Asker Norway	State of Nationality NO	State of Residence NO
Telephone No.		
Facsimile No.		
Teleprinter No.		

## 3. Further observations, if necessary:

4. A copy of this notification has been sent to:
<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority <input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Christine Carrié  Telephone No.: (41-22) 338.83.38
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 44.67810/003	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/03666	International filing date (day/month/year) 05/11/1999	Priority date (day/month/year) 13/11/1998	
International Patent Classification (IPC) or national classification and IPC A61K9/16			
Applicant NYCOMED PHARMA AS et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 09/06/2000	Date of completion of this report 12.02.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Paloniemi Legland, R  Telephone No. +49 89 2399 7315



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03666

## I. Basis for report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):

1-20 as originally filed

Claims No.:

1-21 as originally filed

### Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

the description, pages:  
 the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/03666

the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)      Yes: Claims 1-14  
                      No: Claims 15-21

Inventive step (IS)      Yes: Claims  
                      No: Claims 1-21

Industrial applicability (IA)      Yes: Claims 1-21  
                      No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/03666

**R It m V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: EP-A-0 192 460 (DYNAGRAN ) 27 August 1986 (1986-08-27)

D2: FR-A-2 724 844 (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29)

Claim 1 is directed to a **process** for a preparation of an orally administrable calcium composition, comprising the steps of:

- (i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40  $\mu\text{m}$ , having a crystalline structure and having a surface area of 0,1 to 1,2  $\text{m}^2/\text{g}$ ;
- (ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a **first granulate**;
- (iii) optionally mixing said first granulate with one or more further components to produce a **second granulate**; and
- (iv) optionally compressing said first or second granulate to form tablets.

Document D1, which is regarded to represent the closest prior art, discloses a process for making the agglomerates from which tablets containing up to 75 % of active ingredient are directly compressed. The process of D1 has the same steps as claimed in the process of claim 1 (p.7, I.19-p.9, I.2). Up to 76,6 % of calcium carbonate with a particle size of 3-10  $\mu\text{m}$  as an active ingredient is disclosed in Exp. XIII. D1 differs from the invention by having no specific surface area of calcium compound disclosed. The technical problem was to provide a process for calcium compounds with reduced bulk and with a calcium compound content in excess of 60 % by weight. The solution was the process according to claim 1.

D2 discloses a therapeutic composition and a process for it comprising calcium compound with the same surface area as claimed in claim 1 (Exp. 1; Scoralite 1B). The skilled person confronted with the above mentioned problem and equipped with the

teaching of D1 would have had motivation and technical guidance (D2) for modifying the process of D1 by taking the calcium compound of D2 (Scoralite 1B), since in need of calcium compound with particle size of 3-10 microns, and would have arrived at a process of claim 1. Further dependent claims 2-14 do not contain any features, which in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. These claims merely contain features already known from D1-D2 or typical features generally known to person skilled in the art in the field of processing orally administrable pharmaceutical compositions. Thus the subject-matter of claims 1-14 does not involve an inventive step (Art. 33(3) PCT).

Claim 15 is directed to a **granulate** comprising a fluid bed granulation granulate product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40  $\mu\text{m}$ , having a crystalline structure and having a surface area of 0,1 to 1,2  $\text{m}^2/\text{g}$ . Document D2 discloses a therapeutic composition comprising calcium compound (carbonate), lubricant (magnesium stearate), water-soluble diluent (xylitol/sorbitol), water-soluble binder (polyvinylpyrrolidone) and vitamin D as a further component (Exp. 1; claims 1-8; p.7, I.7-8). The used calcium carbonate is of same type (Scoralite 1B) as used in the examples of the invention, therefore having implicitly same mean particle size and surface area. Consequently, the subject-matter of claims 15-20 is not novel (Art. 33(2) PCT).

Claim 21 is directed to a **tablet** comprising a compressed granulate as claimed above containing: calcium carbonate, vitamin D<sub>3</sub>, a lubricant, citric acid and an oligosaccharide. D2, which is considered to represent the closest prior art, discloses in an Example 1 a tablet comprising most of the features of claim 21. The other features (citric acid and oligosaccharide) are also disclosed in D2 (Exp. 6) being therefore obvious for the skilled man to combine the latter with the former ones. Consequently the subject-matter of claim 21 does not involve an inventive step.

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) and (iii) PCT, the relevant background

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/03666

art has not been indicated in the description and no corresponding documents (D1, D2) have been cited.

The unit "kp" employed on page 14 has not additionally been expressed in terms of the units stipulated by Rule 10.1(a) PCT.

M-H

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>44.67810/003</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/03666</b>	International filing date (day/month/year) <b>05/11/1999</b>	(Earliest) Priority Date (day/month/year) <b>13/11/1998</b>
Applicant <b>NYCOMED PHARMA AS et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  **Certain claims were found unsearchable** (See Box I).

3.  **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03666

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 192 460 A (DYNAGRAN ) 27 August 1986 (1986-08-27)  claims 1-25 page 29; example 13 ---	1-4, 6-11, 15-18
Y	FR 2 724 844 A (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29) claims 1-8 page 3; example 1 ---	1-21
Y	DE 196 17 487 A (MERCK) 6 November 1997 (1997-11-06) claims 1,2,5,7 page 3, line 43 - line 45 example 1 ---	1-21
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

<sup>o</sup> Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

1 February 2000

10/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

## INTERNATIONAL SEARCH REPORT

International Application No

/GB 99/03666

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 487 774 A (BASF) 3 June 1992 (1992-06-03) claim 1 page 1, line 47 - line 49 ----	1-21
P, A	EP 0 931 549 A (GERGELY, GERHARD) 28 July 1999 (1999-07-28) the whole document ----	1-21
A	DATABASE WPI Section Ch, Week 199311 Derwent Publications Ltd., London, GB; Class A, Page 96, AN 1993-088592 XP002129448 & JP 05 032554 A (TEIJIN), 9 February 1993 (1993-02-09) abstract -----	1-21

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/GB 99/03666

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 192460	A	27-08-1986	US	4684534 A	04-08-1987
			AT	66368 T	15-09-1991
			AU	584674 B	01-06-1989
			AU	5377286 A	28-08-1986
			CA	1256028 A	20-06-1989
			DE	3680930 A	26-09-1991
			JP	2540131 B	02-10-1996
			JP	61225119 A	06-10-1986
FR 2724844	A	29-03-1996	AT	177319 T	15-03-1999
			AU	3168395 A	09-04-1996
			CA	2200568 A	28-03-1996
			DE	29521515 U	05-06-1997
			DE	69508263 D	15-04-1999
			DE	69508263 T	04-11-1999
			EP	0785769 A	30-07-1997
			ES	2131845 T	01-08-1999
			FI	971188 A	20-05-1997
			WO	9609036 A	28-03-1996
			HU	77702 A	28-07-1998
			JP	10505850 T	09-06-1998
			NO	971356 A	21-03-1997
			PL	319585 A	18-08-1997
DE 19617487	A	06-11-1997	CN	1216919 A	19-05-1999
			WO	9741835 A	13-11-1997
			EP	0904059 A	31-03-1999
EP 487774	A	03-06-1992	AT	113202 T	15-11-1994
			DE	69013689 D	01-12-1994
			DE	69013689 T	02-03-1995
			DK	487774 T	21-11-1994
EP 931549	A	28-07-1999	NONE		
JP 5032554	A	09-02-1993	JP	2702325 B	21-01-1998



## DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRA

(51) Classification internationale des brevets <sup>6</sup> : <b>A61K 9/00</b>		(11) <b>A1</b>	(43) Date de publication internationale: 28 mars 1996 (28.03.96)
(21) Numéro de la demande internationale: PCT/FR95/01053		(81) Etats désignés: AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LR, LT, LV, MD, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, UG, US, UZ, VN, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) Date de dépôt international: 4 août 1995 (04.08.95)		Publiée <i>Avec rapport de recherche internationale.</i>	
(30) Données relatives à la priorité: 94/11381 23 septembre 1994 (23.09.94) FR			
(71) Déposant ( <i>pour tous les Etats désignés sauf US</i> ): LABORATOIRE INNOTHERA, SOCIETE ANONYME [FR/FR]; 10, avenue Paul-Vaillant-Couturier, F-94111 Arcueil (FR).			
(72) Inventeurs; et			
(75) Inventeurs/Déposants ( <i>US seulement</i> ): MEIGNANT, Catherine [FR/FR]; 42-52, rue de l'Aqueduc, F-75010 Paris (FR). STENGER, Eric [FR/FR]; 10, avenue des Chardons, F-94800 Villejuif (FR).			
(74) Mandataire: DUPUIS-LATOUR, Dominique; Cabinet Bardelle, Pagenberg & Partner, 7, boulevard de Sébastopol, F-75001 Paris (FR).			

(54) Title: THERAPEUTIC VITAMIN-CALCIUM COMBINATION IN UNITARY GALENIC TABLET FORM, METHOD FOR PREPARING SAME AND USE THEREOF

(54) Titre: ASSOCIATION THERAPEUTIQUE VITAMINO-CALCIQUE SOUS FORME GALENIQUE UNITAIRE DE COMPRIMES. SON PROCEDE D'OBENTION ET SON UTILISATION

## (57) Abstract

A therapeutical combination including elemental calcium and at least one vitamin D as the combined active principles, and further containing at least one dry and wet binder combined in a synergistic amount with at least one diluent, at least one binder and at least one lubricant, at least one of said diluent and said binder being a sweetener. The ratio of elemental calcium to vitamin D, expressed in mg of elemental Ca per IU of vitamin D, is advantageously 1-1.5, preferably 1.2-1.3.

## (57) Abrégé

Cette association thérapeutique comprend comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D. Elle renferme en outre au moins un liant à sec et en milieu humide combiné en quantité synergique avec au moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant. Avantageusement, le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5, préférentiellement entre 1,2 et 1,3.

**UNIQUEMENT A TITRE D'INFORMATION**

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publant des demandes internationales en vertu du PCT.

AT	Autriche	GB	Royaume-Uni	MR	Mauritanie
AU	Australie	GE	Géorgie	MW	Malawi
BB	Barbade	GN	Guinée	NE	Niger
BE	Belgique	GR	Grèce	NL	Pays-Bas
BF	Burkina Faso	HU	Hongrie	NO	Norvège
BG	Bulgarie	IE	Irlande	NZ	Nouvelle-Zélande
BJ	Bénin	IT	Italie	PL	Pologne
BR	Brésil	JP	Japon	PT	Portugal
BY	Bélarus	KE	Kenya	RO	Roumanie
CA	Canada	KG	Kirghizistan	RU	Fédération de Russie
CF	République centrafricaine	KP	République populaire démocratique de Corée	SD	Soudan
CG	Congo	KR	République de Corée	SE	Subé
CH	Suisse	KZ	Kazakhstan	SI	Slovénie
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovaquie
CM	Cameroun	LK	Sri Lanka	SN	Sénégal
CN	Chine	LU	Luxembourg	TD	Tchad
CS	Tchécoslovaquie	LV	Lettanie	TG	Togo
CZ	République tchèque	MC	Monaco	TJ	Tadjikistan
DE	Allemagne	MD	République de Moldova	TT	Trinité-et-Tobago
DK	Danemark	MG	Madagascar	UA	Ukraine
ES	Espagne	ML	Mali	US	Etats-Unis d'Amérique
FI	Finlande	MN	Mongolie	UZ	Ouzbékistan
FR	France			VN	Viet Nam
GA	Gabon				

## **Association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, son procédé d'obtention et son utilisation**

5 La présente invention concerne une nouvelle association thérapeutique vitamino-calcique, son procédé d'obtention et son utilisation.

On connaît de nombreuses associations vitamino-calciques pour combattre diverses maladies.

10 Les effets thérapeutiques liés à l'administration conjointe de calcium et de vitamine D sont bien connus, comme cela est relaté par exemple dans les articles de Marie C. Chapuy et coll. — *Effect of Calcium and Cholecalciferol Treatment for Three Years on Hip Fractures in Elderly Women, British Medical Journal, 308*, 1081-1082 (23 avril 1994), de Marie C. Chapuy et coll. — *Vitamin D3 and Calcium to Prevent Hip Fractures in Elderly Women, New England Journal of Medicine, 327*, 1637-1642 (3 décembre 1992) et dans l'article intitulé 15 *Supplementation with Vitamin D3 and Calcium Prevents Hip Fractures in Elderly Women, Nutrition Reviews, Vol. 51, 6*, pp. 183-185.

20 Ces articles montrent également la variabilité des effets thérapeutiques de l'association en fonction du dosage de calcium et de la vitamine D, avec une dose journalière optimale se situant, pour une indication dans la prévention et le traitement de l'ostéoporose, aux alentours de 1000 à 1200 mg de calcium élément et 800 UI de vitamine D3.

Le calcium et la vitamine D sont généralement administrés au patient simultanément, mais sous des formes distinctes, par exemple des comprimés d'un sel de calcium et des gouttes de vitamine D.

En effet, les sels de calcium acceptables du point de vue pharmaceutique et la vitamine D présentent, chacun en ce qui les concerne, des caractéristiques très spécifiques du point de vue de la galénique (voir notamment le EP-A-0 413 828 qui concerne une préparation stabilisée de vitamine D3 destinée à potentialiser la stabilité du principe actif), ce qui conduit à un conditionnement sous des formes séparées.

10 Mais ceci rend difficile le respect des doses absolues et relatives de calcium et de vitamine D, et donc l'observance correcte du traitement, en particulier sur une longue période.

Il a été déjà proposé des associations calcium et vitamine D sous une même forme, par exemple par le WO-A-94 06435 (procédé de traitement gynécologique utilisant notamment une combinaison de vitamine D et de calcium), le WO-A-92 19251 (association de vitamine D avec du calcium pour combattre l'ostéoporose, plus particulièrement sous forme buvable), le EP-A-0 197 514 (composition pharmaceutique comprenant une hormone parathyroïde ou un fragment physiologiquement actif de celle-ci en combinaison avec de la vitamine D hydroxylée ou un sel de calcium non toxique pour augmenter la masse osseuse) ou encore le DE-A-42 12 122 (élément basse calorie à base de protéines, d'un sel de calcium et de vitamine D).

25 Mais dans ces formes connues les proportions entre calcium et vitamine D sont généralement assez éloignées des proportions optimales souhaitables indiquées notamment dans la littérature précitée.

Ces formes connues correspondent d'ailleurs souvent plus à des suppléments vitamino-calciques (suppléments alimentaires ou spécialités "OTC" vendues sans prescription médicale) qu'à de véritables spécialités pharmaceutiques à visée thérapeutique destinées à prévenir ou traiter des affections telles que l'ostéoporose avec une posologie précise.

30 Il existe ainsi à l'heure actuelle un besoin de pouvoir disposer d'une association vitamino-calcique comportant, sous une seule et même forme, un dosage relatif optimal entre calcium et vitamine D, tout particulièrement pour la prévention et le traitement de l'ostéoporose.

Mais du fait de la nature des sels de calcium disponibles acceptables du point de vue pharmaceutique, il est relativement difficile d'associer du calcium sous forme élémentaire avec de la vitamine D dans certains dosages spécifiques. Ceci est particulièrement vrai si l'on désire 5 obtenir des comprimés par un procédé de fabrication par compression directe. Les contraintes des principes actifs, à savoir le calcium sous forme élémentaire et la forme de vitamine D, ne permettent alors pas une mise en oeuvre directe.

La présente invention résout les problèmes mentionnés ci-dessus 10 en proposant une association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisée en ce qu'elle renferme, en outre, au moins un liant à sec et en milieu humide combiné en quantité synergique avec au 15 moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant.

La présente invention a également pour objet un procédé d'obtention 20 d'une association thérapeutique vitamino-calcique comprenant du calcium sous forme élémentaire et au moins une vitamine D, qui est caractérisé en ce qu'il consiste : (a) à granuler le calcium sous forme élémentaire avec un liant à sec et en milieu humide ; (b) à préparer 25 la vitamine D avec un liant édulcorant dans une étape séparée ; (c) à mélanger dans une autre étape séparée un diluant édulcorant, un liant édulcorant supplémentaire et un arôme avec les produits des étapes (a) et (b) tout en ajoutant un lubrifiant ; (d) à comprimer éventuellement le mélange sur presse rotative.

L'invention se rapporte aussi à l'utilisation de la nouvelle association thérapeutique vitamino-calcique pour combattre l'ostéoporose.

L'invention est également relative aux caractéristiques ci-après :

30 — le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5, de préférence entre 1,2 et 1,3 ;

— le calcium sous forme élémentaire provient d'un sel de calcium choisi parmi le carbonate de calcium, le pidolate de calcium, le lactate de calcium, le citrate de calcium, le gluconate de calcium, le 35

chlorure de calcium, le glucoheptonate de calcium, le glycérophosphate de calcium et le phosphate de calcium ;

- la vitamine D est choisie parmi la vitamine D2 ou ergocalciférol, la vitamine D3 ou cholécalciférol ou un mélange de celles-ci ;
- 5 — le comprimé appartient au groupe comprenant les comprimés à croquer, les comprimés sécables, les comprimés à sucer, les comprimés à mâcher, les comprimés dispersibles et les comprimés pour suspension buvable ;
- l'un au moins dudit diluant édulcorant et dudit liant édulcorant est 10 un agent de saveur propre à améliorer les caractéristiques gustatives de l'association, avantageusement un polyol, notamment choisi parmi le mannitol, le sorbitol, le xylitol et le maltitol ;
- le liant à sec et en milieu humide est choisi parmi une cellulose, la maltodextrine et la polyvinylpyrrolidone ;
- 15 — le lubrifiant est choisi parmi le stéarate de magnésium, l'acide stéarique, l'huile de ricin hydrogénée, l'huile de coton hydrogénée et le bhéname de glycérol ;
- l'association renferme en outre un agent aromatisant et/ou un acidifiant et/ou un édulcorant supplémentaire choisi parmi le saccharinate de sodium, le cyclamate de sodium et l'aspartame ;
- 20 — l'association vitamino-calcique répond à la formule générale :

Calcium (carbonate de)	1 250 mg
(Quantité correspondant à calcium élément)	500 mg)
Cholécalciférol	4 mg *
25 Xylitol	661 mg
Sorbitol	500 mg
Polyvinylpyrrolidone	45 mg
Arôme (citron, orange, etc.)	20 mg
30 Stéarate de magnésium	20 mg

(\* Vitamine D3 dosée à 100 000 UI/g),  
ladite formule correspondant à un comprimé terminé à 2 500 mg.



sortiront d'un exemple de réalisation ci-après.

Dans cet exemple, l'association de l'invention se présente sous forme d'un comprimé à croquer de formule suivante (pour un comprimé terminé à 2500 mg) :

5

	Calcium (carbonate de)	1 250 mg
	(Quantité correspondant à calcium élément)	500 mg)
	Cholécalciférol	4 mg *
	Xylitol	661 mg
10	Sorbitol	500 mg
	Polyvinylpyrrolidone	45 mg
	Arôme (citron, orange, etc.)	20 mg
	Stéarate de magnésium	20 mg

(\* Vitamine D3 dosée à 100 000 UI/g)

15

Le carbonate de calcium est du type SCORALITE 1B<sup>®</sup>, SCORA ; il s'agit d'une poudre blanche de granulométrie très fine d'un diamètre moyen de 12 micromètres environ, de densité élevée ( $d = 1,3 \text{ g/cm}^3$  environ) présentant un mauvais écoulement et une mauvaise aptitude à la compression.

La vitamine D est du cholécalciférol (type 100 CWS<sup>®</sup>, ROCHE) ; il s'agit d'une poudre granuleuse, de diamètre moyen de 200 micromètres environ, de couleur jaunâtre, dosée à 100 000 UI par gramme.

La présence de DL- $\alpha$ -tocophérol (environ 0,2 % m/m de vitamine E) lui confère une grande stabilité et empêche son oxydation.

Le diluant-édulcorant utilisé dans l'invention est de préférence du xylitol de type XYLITAB 300<sup>®</sup>, FINNSUGAR. Ce xylitol est un polyol de saveur sucrée (équivalente à celle du saccharose), procurant une agréable sensation de fraîcheur dans la bouche, il est acariogène et très peu calorique (2,4 Kcal/g contre 4 Kcal/g pour le saccharose). Cette sensation agréable permet une meilleure observance du traitement par le patient. Ce xylitol utilisé possède des propriétés de comprimabilité supérieures à celles du xylitol standard.

Ce composé se présente sous la forme d'une poudre granuleuse, cristalline blanche, d'un diamètre moyen de 250 micromètres.

Le liant-édulcorant utilisé dans la présente invention est en particulier du sorbitol (de type NEOSORB P 60 W<sup>®</sup>, ROQUETTE). Ce polyol se présente sous la forme d'une poudre granuleuse blanche, d'un diamètre moyen de 200 micromètres et possède d'excellentes propriétés liantes 5 en compression. Le sorbitol est de saveur sucrée (70 % de celle du saccharose), acariogène et peu calorique (2,4 Kcal/g).

Le liant de la présente invention est, de préférence, de la polyvinyl-pyrrolidone (de type KOLLIDON K 30<sup>®</sup>, BASF) ; il se présente sous la forme d'une poudre blanchâtre granuleuse et possède de très grandes propriétés liantes en granulation humide. La valeur de la constante K 10 caractérise les polyvinylpyrrolidones solubles et dépend de leur solubilité relative.

L'aromatisant est particulièrement un arôme citron (SBI) ; il se présente sous forme d'une poudre fine, jaunâtre, composée d'huiles essentielles atomisées sur de la maltodextrine. De nombreux essais réalisés 15 durant la mise en oeuvre de la présente invention qui ont comparé différents arômes ont montré que l'arôme citron convenait parfaitement bien au masquage du goût crayeux du carbonate de calcium et qu'il s'associait agréablement à la sensation de fraîcheur apportée par 20 le xylitol.

Le lubrifiant est généralement du stéarate de magnésium se présentant sous forme d'une poudre fine, blanchâtre, permettant d'éviter le phénomène de grippage au niveau des matrices des presses à comprimer quand l'association vitamino-calcique de la présente invention 25 est sous forme de comprimés.

La quantité de calcium élémentaire par prise sera, de préférence, de 500 mg, ce qui correspond à 1250 mg de carbonate de calcium.

La quantité de cholécalciférol est de 4 mg par prise, ce qui correspond 30 à 400 UI d'une vitamine D3 dosée à 100 000 UI/g. En pratique, la quantité de cholécalciférol par comprimé dépend du dosage de la matière première utilisée.

Ces doses correspondent notamment à la posologie optimale indiquée par les publications mentionnées plus haut, tant en valeur absolue (doses journalières de calcium et de vitamine D3, respectivement) 35 que relative (ratio calcium/vitamine de l'ordre de 1,25 mg de Ca élé-

ment par UI de vitamine D).

Les nombreux essais des formules de cet exemple ont permis d'optimiser les quantités des différents excipients.

Pour obtenir un comprimé à croquer au goût le plus agréable, l'ap-  
5 port en liant à sec et en milieu humide combiné en quantité synergique avec au moins le diluant édulcorant, au moins le liant édulcorant et au moins le lubrifiant doit être important. Dans le cas d'un comprimé, celui-ci aura généralement une masse de 2500 mg.

Dans certaines formes de mise en oeuvre de la présente invention,  
10 on utilise une quantité de xylitol d'environ 661 mg, qui correspond à la quantité nécessaire à incorporer pour obtenir le meilleur masquage de goût du carbonate de calcium sans pour autant diminuer la comprimabilité du mélange, les propriétés du xylitol en compression étant moyennes.

15 Le sorbitol est utilisé à raison d'environ 500 mg car il s'agit de la quantité nécessaire à incorporer pour obtenir une parfaite reproductibilité de la fourchette de résistance à la rupture, paramètre critique dans le cas des comprimés à croquer. Une quantité supérieure, au détriment du xylitol, diminuerait les qualités gustatives du comprimé.

20 La polyvinylpyrrolidone est utilisée à raison d'environ 45 mg, lors de la granulation humide du carbonate de calcium, une partie (20 mg) est mélangée à sec avec le carbonate de calcium, la partie restante (25 mg) est utilisée en solution à 10 % dans de l'eau déminéralisée à froid. Une teneur en polyvinylpyrrolidone inférieure à 40 mg entraîne 25 une trop grande friabilité des grains de carbonate de calcium. Une quantité plus importante n'apporte pas de réels bénéfices.

La quantité d'arôme citron est d'environ 20 mg, il s'agit de la quantité nécessaire pour aromatiser de façon satisfaisante le comprimé. Une faible variation de cette quantité ( $\pm 3$  mg) ne modifie pratiquement pas 30 le goût final.

La quantité de stéarate de magnésium est d'environ 20 mg. Il s'agit de la quantité nécessaire pour obtenir une lubrification satisfaisante lors de la compression. Une quantité plus faible, environ 15 mg, entraîne un phénomène de grippage, alors qu'une quantité supérieure, 25 mg 35 tend à diminuer la dureté du comprimé et risque de modifier son goût.

Les caractéristiques physiques des éléments de l'association vitamino-calcique de la présente invention vont être indiquées ci-après.

Le carbonate de calcium a un écoulement nul et une densité apparente ( $\text{g/cm}^3$ ) d'environ 1,28 à 1,35 et une humidité résiduelle en pour-cent de 0,1. La vitamine D3 cholécalciférol sous forme d'un concentrat de forme pulvérulente a un écoulement de 6 secondes pour 100 g de poudre, une densité apparente en  $\text{g/cm}^3$  de 0,73, une humidité résiduelle en pour-cent de 6,4 et un dosage en  $\text{UI/g}$  de 100 000.

Le xylitol a un écoulement nul, une densité apparente en  $\text{g/cm}^3$  d'environ 0,68-0,69, une humidité résiduelle en pour-cent de 0,2 à 0,3.

Le sorbitol a des écoulements dans la gamme de 4 à 5 secondes pour 100 g de poudre, une densité apparente en  $\text{g/cm}^3$  de 0,71 à 0,73 et une humidité résiduelle en pour-cent de 0,5 à 0,8.

Les étapes de mise en oeuvre préférées du procédé d'obtention de l'association vitamino-calcique de la présente invention vont maintenant être exposées.

Une granulation humide du carbonate de calcium est tout d'abord effectuée.

Dans cette mise en oeuvre, le carbonate de calcium et la polyvinylpyrrolidone sont tamisés sur un tamiseur vibrant pourvu d'une grille d'ouverture de maille appropriée ; ces poudres sont introduites dans un mélangeur et mélangées peu de temps à une vitesse appropriée. De la solution de polyvinylpyrrolidone est ajoutée par étapes successives. Une granulation est effectuée jusqu'à l'obtention d'une masse humide, permettant une étape de précalibrage suivante.

Une précalibration est effectuée sur un granulateur muni d'une grille d'ouverture de maille appropriée.

Le produit résultant est séché sur un lit d'air fluidisé et laissé à refroidir.

La perte de masse à la dessiccation est déterminée et une calibration sur une grille d'ouverture de maille appropriée est effectuée.

Parallèlement, la vitamine D3 est prémélangée et, après un tamisage, elle est mélangée avec du sorbitol dans un mélangeur pendant une durée appropriée et à une vitesse de rotation convenable.

On réalise ensuite le mélange avec les autres constituants en tamisage.

sant du xylitol, du sorbitol et l'arôme sur un tamis vibrant équipé d'une grille à ouverture de mailles appropriée. On mélange ces trois constituants avec le prémélange de vitamine D3-sorbitol dans un mélangeur à une vitesse appropriée. On introduit ensuite le carbonate de calcium granulé et on le mélange pendant la durée requise à la vitesse appropriée.

Le stéarate de magnésium est tamisé sur un tamis vibrant muni d'une grille d'ouverture de maille appropriée puis l'ensemble est mélangé dans un mélangeur.

10 L'ensemble ci-dessus peut être ensuite comprimé sur une presse à comprimer en contrôlant régulièrement l'uniformité de la masse et la résistance à la rupture. Les durées de mélange, les vitesses de rotation et les dimensions des tamis sont classiques et sont bien connues de l'homme du métier.

15 Ainsi, la présente invention permet d'obtenir une association vitamino-calcique contenant 500 mg de calcium élémentaire et 4 mg de vitamine D3 par prise, association qui est notamment sous la forme d'un comprimé à croquer qui est d'un goût agréable et d'une dureté adaptée aux patients.

20 Plus particulièrement, à titre d'exemple non limitatif, les doses qui seront généralement utilisées se situeront dans les gammes suivantes : calcium sous forme élémentaire, environ 500 mg à environ 1500 mg ; vitamine D ou mélange de vitamines D, environ 3,5 mg à environ 12 mg. Une telle association vitamino-calcique, notamment sous forme de comprimés, ne contient ni sucre ni sodium.

25 Cependant, d'autres formes galéniques sont possibles.

On peut ainsi réaliser un comprimé sécable (à avaler) de formule suivante, pour un comprimé de 1,60 g :

30	Carbonate de calcium	1,250 g
	Vitamine D3	0,004 g
	Cellulose microcristalline	0,236 g
	Polyvinylpyrrolidone	0,040 g
	Stéarate de magnésium	0,020 g

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De façon générale, pour la mise en oeuvre de comprimés du type à croquer ou à sucer on utilisera du carbonate de calcium. D'autres sels tels que le triphosphate de calcium peuvent être utilisés, mais leur absorption par l'organisme est moindre, ce qui conduit à adapter les 5 quantités en conséquence (pour une même quantité de calcium élémentaire absorbé, il faut environ 1,2 g de triphosphate de calcium pour 1 g de carbonate de calcium).

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## REVENDICATIONS

1. Association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés, comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisée en ce qu'elle renferme, en outre, au moins un liant à sec et en milieu humide combiné en quantité synergique avec au moins un diluant, au moins un liant et au moins un lubrifiant, l'un au moins dudit diluant et dudit liant étant un édulcorant.  
10
2. Association selon la revendication 1, où le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1 et 1,5.
- 15 3. Association selon la revendication 2, où le rapport du calcium sous forme élémentaire à la vitamine D, exprimé en mg de Ca élément par UI de vitamine D, est compris entre 1,2 et 1,3.
- 20 4. Association selon la revendication 1, où le calcium sous forme élémentaire provient d'un sel de calcium choisi parmi le carbonate de calcium, le pidolate de calcium, le lactate de calcium, le citrate de calcium, le gluconate de calcium, le chlorure de calcium, le glucoheptonate de calcium, le glycérophosphate de calcium et le phosphate de calcium.
- 25 5. Association selon la revendication 1, où la vitamine D est choisie parmi la vitamine D2 ou ergocalciférol, la vitamine D3 ou cholécalciférol ou un mélange de celles-ci.
- 30 6. Association selon la revendication 1, où le comprimé appartient au groupe comprenant les comprimés à croquer, les comprimés sécables, les comprimés à sucer, les comprimés à mâcher, les comprimés dispersibles et les comprimés pour suspension buvable.
- 35 7. Association selon la revendication 1, où l'un au moins dudit diluant édulcorant et dudit liant édulcorant est un agent de saveur pro-

pre à améliorer les caractéristiques gustatives de l'association.

8. Association selon la revendication 7, où l'un au moins dudit diluant édulcorant et dudit liant édulcorant est un polyol.

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9. Association selon la revendication 8, où le polyol est choisi parmi le mannitol, le sorbitol, le xylitol et le maltitol.

10. Association selon la revendication 1, où le liant à sec et en milieu humide est choisi parmi une cellulose, la maltodextrine et la polyvinylpyrrolidone.

11. Association selon la revendication 1, où le lubrifiant est choisi parmi le stéarate de magnésium, l'acide stéarique, l'huile de ricin hydrogénée, l'huile de coton hydrogénée et le béhenate de glycérol.

12. Association selon la revendication 1, renfermant en outre un agent aromatisant.

20 13. Association selon la revendication 1, renfermant en outre un acidifiant.

25 14. Association selon la revendication 1, renfermant en outre un édulcorant supplémentaire choisi parmi le saccharinate de sodium, le cyclamate de sodium et l'aspartame.

15. Association selon la revendication 3, de formule générale :

Calcium (carbonate de)	1 250 mg
(Quantité correspondant à calcium élément)	500 mg)
Cholécalciférol	4 mg *
Xylitol	661 mg
Sorbitol	500 mg
Polyvinylpyrrolidone	45 mg
Arôme (citron, orange, etc.)	20 mg
35 Stéarate de magnésium	20 mg

(\* Vitamine D3 dosée à 100 000 UI/g),  
ladite formule correspondant à un comprimé terminé à 2 500 mg.

16. Procédé d'obtention d'une association thérapeutique vitamino-calcique sous forme galénique unitaire de comprimés comprenant comme principes actifs associés du calcium sous forme élémentaire et au moins une vitamine D, caractérisé en ce qu'il consiste :

- (a) à granuler le calcium sous forme élémentaire avec un liant à sec et en milieu humide ;
- 10 (b) à prémélanger la vitamine D avec un liant édulcorant dans une étape séparée ;
- (c) à mélanger dans une autre étape séparée un diluant édulcorant, un liant édulcorant supplémentaire et un arôme avec les produits des étapes (a) et (b) tout en ajoutant un lubrifiant ;
- 15 (d) à comprimer éventuellement le mélange sur presse rotative.

17. L'utilisation de l'association thérapeutique vitamino-calcique de l'une des revendications 1 à 15 pour combattre l'ostéoporose.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/FR 95/01053A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 413 828 (TEIJIN LIMITED) 27 February 1991 see claims 1-7 see page 2, line 11 - line 19 see page 5, line 5 - line 29 -----	1,4-17

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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1 Date of the actual completion of the international search  31 October 1995	Date of mailing of the international search report  17. 11. 95
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Ventura Amat, A

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Int'l Application No

**PCT/FR 95/01053**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-413828	27-02-91	JP-A- 2229115	11-09-90
		CA-A- 2027592	02-09-90
		WO-A- 9009796	07-09-90
		KR-B- 9310621	02-11-93
		US-A- 5158944	27-10-92

# RAPPORT DE RECHERCHE INTERNATIONALE

De la Internationale No

PCT/FR 95/01053

**A. CLASSEMENT DE L'OBJET DE LA DEMANDE**  
CIB 6 A61K9/00

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

**B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE**

Documentation minimale consultée (système de classification suivi des symboles de classement)  
CIB 6 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche utilisés)

**C. DOCUMENTS CONSIDERES COMME PERTINENTS**

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	<p>EP,A,0 413 828 (TEIJIN LIMITED) 27 Février 1991          voir revendications 1-7          voir page 2, ligne 11 - ligne 19          voir page 5, ligne 5 - ligne 29          -----</p>	1,4-17

Voir la suite du cadre C pour la fin de la liste des documents

Les documents de familles de brevets sont indiqués en annexe

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**RAPPORT DE RECHERCHE INTERNATIONALE**

Renseignements relatifs aux membres de familles de brevets

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Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP-A-413828	27-02-91	JP-A- 2229115 CA-A- 2027592 WO-A- 9009796 KR-B- 9310621 US-A- 5158944	11-09-90 02-09-90 07-09-90 02-11-93 27-10-92

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 <b>(21) International Application Number:</b> PCT/GB99/03666 <b>(22) International Filing Date:</b> 5 November 1999 (05.11.99)  <b>(30) Priority Data:</b> 9825033.5 13 November 1998 (13.11.98) GB		 <b>(81) Designated States:</b> AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
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**(54) Title:** PROCESS FOR PREPARING ORAL CALCIUM COMPOSITIONS**(57) Abstract**

The invention provides a process for the preparation of an orally administrable calcium composition, said process comprising the steps of: (i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g; (ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate; (iii) optionally mixing said first granulate with one or more further components to produce a second granulate; and (iv) optionally compressing said first or second granulate to form tablets.

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Process for preparing oral calcium compositions

5        This invention relates to a process for the manufacture of an orally administrable pharmaceutical composition containing a physiologically tolerable calcium compound, in particular a composition in tablet form.

10      Calcium carbonate tablets are used as a source of calcium, especially for patients suffering from or at risk of osteoporosis. Moreover calcium carbonate is used as an acid neutralizing agent in antacid tablets.

15      Calcium carbonate is used in such tablets since the calcium content of calcium carbonate is high, the calcium is presented in a form which can be taken up from the gastrointestinal tract, calcium carbonate is effective at neutralizing gastric acids, and calcium carbonate is a physiologically acceptable calcium compound.

20      In such tablets, various binders, sweeteners and flavors are used in order to produce a tablet which is readily acceptable to the patient. Indeed many producers have sought to achieve improved patient acceptability by formulating the tablets with such excipients in a "chewable" form. As a result, and since the daily recommended dosage is generally about 1000 mg calcium, the commercially available calcium tablets which commonly contain 500 mg calcium are relatively bulky.

25      Examples of chewable calcium carbonate tablets are described in WO 96/09036 (Laboratoire Innothera) and in US-A-4446135 (Sterling Drug). The chewable calcium carbonate tablets described in these two patent publications have a calcium carbonate content of about 50% or less by weight and for a 500 mg calcium dosage are therefore undesirably large.

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The present invention is directed to a process by which this undesired bulk may be reduced, and in particular to a process by which a chewable calcium tablet may be produced with a calcium compound content in excess of 60% by weight.

Thus viewed from one aspect the present invention provides a process for the preparation of an orally administrable calcium composition, said process comprising the steps of:

(i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a specific surface area of 0.1 to 1.2 m<sup>2</sup>/g, preferably 0.2 to 0.9 m<sup>2</sup>/g, especially 0.3 to 0.8 m<sup>2</sup>/g;

(ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate;

(iii) optionally mixing said first granulate with one or more further components to produce a second granulate, preferably a granulate having a content of said calcium compound of at least 60% by weight; and

(iv) optionally compressing said first or second granulate to form tablets.

The physical characteristics of the calcium compound used in the process of the invention are important in order that the fluid bed granulation stage should produce a first granulate having the desired characteristics. The calcium compound should be crystalline and have a mean particle size of 3 to 40 $\mu$ m, preferably 5 to 30 $\mu$ m. Preferably it should have a bulk density in the range of 0.2 to 1.5g/mL, more preferably 0.3 to 1.4g/mL, especially 0.4 to 1.3g/mL. The calcium compound is preferably an acid soluble compound, e.g. a compound poorly soluble or insoluble in water at pH7 but soluble in water at gastric pH values.

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The upper particle size limit of  $40\mu\text{m}$  is important in order to avoid a gritty mouthfeel in the final product. The lower particle size limit of  $3\mu\text{m}$  is also important in order to avoid a feeling of stickiness on the teeth during chewing.

Crystallinity, in particular the possession of relatively smooth crystal surfaces and low specific surface area, is important for the achievement of effective and rapid wetting and granulation in the fluid granulation step of the process of the invention.

Specific surface area may be determined using apparatus such as the Carlo Erba Sorptomatic 1900.

The calcium compound may, for example, be selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate (e.g. in tribasic, dibasic or monobasic forms, i.e.  $\text{Ca}_3(\text{PO}_4)_2$ ,  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$  and  $\text{Ca}(\text{HPO}_4)_2 \cdot \text{H}_2\text{O}$ ), calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof. However, calcium carbonate, in particular in calcite form, is preferred due to its high calcium content, its ready availability, its cost, its well-documented absorption characteristics in humans, and its performance in the fluid granulation step of the process of the invention.

Especially, preferably calcium carbonate having individual or primary and cubic or pseudo-cubic shaped calcite crystals with smooth or even surfaces are used. Desirably such crystals are also transparent. Where the end product is for use as a medicine, it is also preferred that the calcium carbonate be a material precipitated according to Ph. Eur.

Examples of appropriate commercially available calcium carbonate include Merck 2064 (available from Merck, Darmstadt, Germany), Scoralite 1A and Scoralite 1B (available from Scora Watrigant SA, France), Super-Purity  $\text{CaCO}_3$  and Medicinal Heavy  $\text{CaCO}_3$  (available from

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Shanghai Da Yu Biochemistry Co. Ltd., China), and Pharmacarb LL (available from Crompton & Knowles, Vineland, USA). Scoralite 1B and Scoralite 1A + 1B are particularly preferred. Merck 2064 has a mean particle size of 10 to 30 $\mu$ m, an apparent bulk density of 0.4 to 0.7 g/mL, and a specific surface area of 0.3 m<sup>2</sup>/g; Scoralite 1A has a mean particle size of 5 to 20 $\mu$ m, an apparent bulk density of 0.7 to 1.0 g/mL and a specific surface area of 0.6 m<sup>2</sup>/g; Scoralite 1A + 1B has a mean particle size of 7 to 25  $\mu$ m, an apparent bulk density of 0.7 to 1.2 g/mL and a specific surface area of 0.35 to 0.8 m<sup>2</sup>/g; Scoralite 1B has a mean particle size of 10 to 30 $\mu$ m, an apparent bulk density of 0.9 to 1.3 g/mL and a specific surface area of 0.4 to 0.6 m<sup>2</sup>/g; Medicinal Heavy CaCO<sub>3</sub> has a mean particle size of 5 to 30  $\mu$ m, an apparent bulk density of 0.9 to 1.3 g/mL and a specific surface area of 0.8 m<sup>2</sup>/g; Super-Purity CaCO<sub>3</sub> has a mean particle size of 10 to 30  $\mu$ m, an apparent bulk density of 0.9 to 1.2 g/mL and a specific surface area of 0.6 m<sup>2</sup>/g; and Pharmacarb LL has a mean particle size of 5 to 30  $\mu$ m, an apparent bulk density of 0.8 to 1.2 g/mL and a specific surface area of 0.7 m<sup>2</sup>/g. The Pharmacarb LL calcium carbonate however is not apparently a material precipitated in accordance with Ph. Eur. and thus is more preferred for production of end products which are for use as dietary supplements or food products than those which are for use as pharmaceuticals.

The calcium compound or mixture of calcium compound preferably makes up 60 to 95% by weight of the second granulate, and preferably provides a calcium content of 15 to 40%, more especially 20 to 35%, and still more especially 25 to 30% by weight in the second granulate.

The calcium compound or mixture of compounds preferably makes up 60.5 to 96%, more preferably 66 to 91% still more preferably 68 to 80% and most preferably 72 to 76% by weight of the first granulate.

The water-soluble diluent used in step (ii) of the

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process of the invention is preferably a sweetener or a mixture of sweeteners, e.g. a polyol or a polysaccharide, more preferably a non-cariogenic sweetener. Examples of suitable diluents include 5 sorbitol, xylitol, isomalt and mannitol, which are non-cariogenic. Neosorb P100T sorbitol, xylitol CM50 and isomalt PF are available commercially from Roquette Freres, Xyrofin and Palatinit respectively. Further examples of suitable saccharide-based diluents include 10 sucrose, fructose and the maltodextrins (e.g. Lycatab DSH available from Roquette Freres). Especially preferred as diluents are the non-cariogenic oligosaccharides such as inulin and oligofructose. Inulin may be obtained by extraction from chickory root 15 and is available under the trade name Raftiline from Orafti SA, Tieren, Belgium. Oligofructose is obtained by partial hydrolysis of inulin and is available from Orafti SA under the trade name Raftilose and from Beghin-Meiji Industries, Neuilly-sur-Seine, France under 20 the trade name Actilight.

The diluent preferably makes up the major proportion, e.g. by 70 to 96%, more preferably 80 to 95%, still more preferably 85 to 94%, most preferably 90 to 92% of the total weight of diluent and binder in the 25 first granulate.

The calcium compound and diluent (which, especially in the case of inulin, may be the same material as is used as the binder) are preferably blended before addition of the aqueous binder. The blending may 30 conveniently be performed as a dry blending, for example using a blender with a rotating mixer arm, e.g. a blade. This ensures that any lumps are removed and achieves an intimate mixing of the calcium compound and the diluent. By way of example, a high speed mixer (e.g. Fielder PMA 35 25/2G) may be used operating at maximum speed for both the impeller and knife for two minutes; however any mill may be used to break up lumps in the mixture and indeed

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the calcium compound and the diluent may be treated in this way separately to remove lumps before they are blended.

5 The water-soluble binder used in step (ii) of the process of the invention may be selected from known water-soluble pharmaceutical binders, e.g. it may be a soluble cellulose or polysaccharide or a polyvinylpyrrolidone or a mixture thereof. Preferably the binder is a polyvinylpyrrolidone, e.g. Kollidon K30, 10 Kollidon 90F or Kollidon VA64 which are available commercially from BASF. Inulin and maltodextrin may also be used as binders.

15 The binder is preferably used in aqueous solution at a concentration of 10 to 35% by weight, more especially 15 to 35%, preferably 25 to 30%, and particularly 27 to 29% by weight.

20 The fluid granulation step, step (ii) of the process of the invention, may be effected in any fluid granulation apparatus, e.g. a Glatt GPCG 3 fluid bed available from Glatt GmbH. The procedure preferably involves spraying the aqueous binder mixture onto the fluidized diluent/calcium compound mixture. Fluidization may be achieved by gas flow through the mixture or alternatively mechanically, e.g. by the use 25 of counter-rotating, interlocking paddles with horizontal rotational axes. The liquid sprayed is preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C) and the particulate onto which it is sprayed is again preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C). The gas pressure of the spray chamber is conveniently ambient (e.g. 1 atmosphere). The spray rate may be 30 adjusted, according to batch size and component identities and concentrations, to optimize the mean particle size of the first granulate. However, for a 35 3kg solids batch, a spray rate of 30 to 50g/min may be

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appropriate and a spray rate of about 40g/min is particularly preferred.

The granulate may be dried in a separate drier but preferably is dried in place in the fluidized bed mixer, e.g. using a heated gas (e.g. air) flow through the granulate. This can be effected while spraying of the binder solution is taking place or after spraying of the binder solution has been completed. Clearly if drying is effected during spraying it should be completed after spraying has stopped. Preferably a drying gas temperature of 60 to 90°C, more especially 65 to 75°C, in particular about 70°C is used. Particularly preferably drying is effected such that the granulate temperature reaches 40 to 50°C, especially about 43 to 45°C.

In this way a first granulate having a low water content, e.g. 1 to 5% by weight, preferably about 3%, may be produced and subsequently dried to a moisture content of about 0.1 to 0.5%, preferably 0.2% by weight, within an overall granulation and drying period of 15 to 45 mins, preferably 20 to 30 mins.

The first granulate preferably has a particle size distribution (as determined by Malvern particle size analysis) as follows:

$$D(v, 0.1) = 15-21 \mu\text{m}$$

$$D(v, 0.5) = 70-120 \mu\text{m}$$

$$D(v, 0.9) = 190-330 \mu\text{m}$$

Where the first granulate is to be mixed with further components before tabletting, such further components will typically be one or more of the following: further active agents, e.g. vitamins, in particularly vitamin D, especially vitamin D<sub>3</sub>; effervescent agents; diluents; sweeteners; flavors; acidulants; and lubricants, e.g. hydrogenated fatty acids, polyethyleneglycol, sodium stearyl fumarate, stearic acid and salts thereof, for example magnesium stearate. When a further active agent is added, this should be at a therapeutically effective dosage. When

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vitamin D is added, e.g. to produce a product suitable for treatment or prophylaxis of osteoporosis, this preferably is at a calcium to vitamin D ratio of 100 mg Ca: 30 to 150 IU Vitamin D, especially 100:35 to 100 IU, 5 more especially 100:40 to 90 IU. Preferably the second granulate should be such as to be tablettable to produce tablets containing 500mg Ca and 200 to 250 IU or 400 to 450 IU vitamin D<sub>3</sub>.

Where vitamin D is used, this may conveniently be 10 vitamin D<sub>2</sub> (ergocalciferol) or more preferably vitamin D<sub>3</sub> (cholecalciferol). Dose units of the second granulate, e.g. tablets formed therefrom, preferably contain 250 to 1500mg Ca and 5 to 30 $\mu$ g vitamin D.

Vitamin D<sub>3</sub> is commercially available from Roche in a 15 granular form which consists of vitamin D<sub>3</sub> in edible fats finely dispersed in a starch coated matrix of gelatin and sucrose with D,L- $\alpha$ -tocopherol added as an antioxidant. However, other dry powder or granulate forms of vitamin D may also be used.

20 A chewable tablet containing 500 mg calcium and 5  $\mu$ g vitamin D<sub>3</sub> only contains 2.2 mg of the commercial quality of vitamin D<sub>3</sub> from Roche (100 CWS). This constitutes only 0.13% of the total weight of the tablet and one may thus anticipate problems with the 25 homogeneity of vitamin D<sub>3</sub> in the tablet. A Malvern particle size analysis of the 100 CWS quality typically gives the following results for the particle size distribution: D(v, 0.1)=180-250  $\mu$ m, D(v, 0.5)=240-300  $\mu$ m and D(v, 0.9)=320-400  $\mu$ m. It has been found desirable 30 to sieve the vitamin D<sub>3</sub> on 60 mesh (250  $\mu$ m) with a Russell vibrating sieve. This procedure will increase the number of vitamin D<sub>3</sub> particles per tablet and thus facilitate a more even and uniform distribution. In addition to this the sieving procedure will also 35 eliminate all the coarse particles in the vitamin D<sub>3</sub>, which also contribute to an inhomogeneous distribution.

Twenty consecutive batches of a chewable tablet

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containing 500 mg calcium and 5 µg vitamin D<sub>3</sub> have been produced which have utilized a sieved (< 60 mesh) vitamin D<sub>3</sub> with a mean particle size in the region of 203-217 µm. All twenty batches comply with the 5 requirements set in the European Pharmacopeia with respect to the uniformity of content of vitamin D<sub>3</sub> in the tablet.

Other active ingredients can be included in the compositions produced according to the invention. 10 Examples include isoflavones, vitamin K, vitamin C, vitamin B<sub>6</sub> and oligosaccharides such as inulin and oligofructose. Isoflavones exhibit a weak oestrogenic effect and can thus increase bone density in post-menopausal women. Isoflavones are available under the 15 trade name Novasoy 400 from ADM Nutraceutical, Illinois, USA. Novasoy 400 contains 40% isoflavones and will typically be used in an amount sufficient to provide 25 to 100 mg isoflavone/dosage. Isoflavones may be included in the second granulate; however as Novasoy 400 20 is a relatively cohesive powder it is preferred that it be included in the first granulate in order to ensure that it is uniformly distributed. Vitamin K (more especially vitamin K<sub>1</sub>) may improve biochemical markers of bone formation and bone density and low concentrations 25 of vitamin K<sub>1</sub> have been associated with low bone mineral density and bone fractures. Vitamin K<sub>1</sub> is available from Roche as Dry Vitamin K<sub>1</sub>, 5% SD, a dry substance containing 5% vitamin K<sub>1</sub>. Typically vitamin K<sub>1</sub> will be used in a quantity sufficient to provide 0.05 to 5 mg 30 vitamin K<sub>1</sub>/dosage. Vitamin C and vitamin B<sub>6</sub> (available from Roche, Takeda and BASF amongst others) function as co-factors in the formation of collagen, the main component of the organic matrix of bone. Vitamin C and vitamin B<sub>6</sub> will typically be used in quantities 35 sufficient to provide 60 to 200 mg vitamin C/dosage and 1.6 to 4.8 mg vitamin B<sub>6</sub>/dosage respectively. Oligosaccharides have been shown to facilitate and

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increase calcium absorption and may typically be used in quantities sufficient to provide 0.3 to 5 g oligosaccharide/dosage. In general it is desirable that a total of at least 5g oligosaccharide is administered 5 daily to facilitate calcium uptake and to obtain a prebiotic effect.

Where an active component is used which forms a minor part of the overall granulate, e.g. vitamin D, it is general preferred to produce a premix of such a component and the first granulate before mixing the premix and the remaining required quantity of the first granulate. This ensures uniform distribution of the minor component in the second granulate.

The second granulate also preferably contains a flavor, e.g. a fruit flavor, in particular a lemon or orange flavor, in order to mask the chalky taste of calcium carbonate. The flavor may, for example, be a lemon or orange oil dispersed in a hydrogenated glucose syrup material or, alternatively, it may be any other stable flavor, e.g. one of the Durarome flavors available from Firmenich.

Extra sweeteners, e.g. artificial sweeteners such as aspartame, acesulfame K, saccharin, sodium saccharin, neohesperidine hydrochloride, taumatin and sodium 25 cyclamate may be used to enhance the sweetness of the granulate.

Acidulants, e.g. anhydrous citric acid, malic acid, or any other organic acid with suitable organoleptic properties may be used in order to complement and 30 enhance the flavour and sweetness of the dosage form.

Such extra components may be mixed in during the fluid granulation step of the process of the invention, but preferably they are mixed in with the first granulate in a separate dry mixing step, optionally 35 after a sieving step to ensure homogeneous mixing.

When the granulate is to be tabletted, it preferably includes a lubricant, e.g. magnesium

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5 stearate, stearic acid, hydrogenated fatty acids, sodium stearyl fumarate, PEG 6000 or PEG 8000. Magnesium stearate is generally preferred. Such a lubricant will generally make up 0.3 to 1.5%, particularly 0.35 to 1.0% by weight of the composition to be tabletted. The lubricant is preferably added in a final mixing step and mixed in for a brief time to prevent overmixing and subsequent lack of cohesion in the tabletted product.

10 Where the granulate is to be tabletted, this can be effected on conventional tablet presses. Preferably the tablet so produced will have a total weight of 500 to 3800mg, e.g. 500 to 3000 mg, more especially 1000 to 2500mg, most preferably 1500 to 2000mg. If desired however, the granulate (either the first granulate or 15 the second granulate) may be used for other administration forms, e.g. powders, capsules, lozenges, coated tablets, etc. In general dose units (e.g. tablets or sachet contents) will contain 100 to 1000 mg Ca, especially 250 to 750 mg Ca, most preferably 450 to 20 550 mg Ca. The granulate is itself novel and forms a further aspect of the invention. Viewed from this aspect, the invention provides a granulate, preferably a tablettable granulate, comprising a fluid bed granulation granulate product of a physiologically 25 tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g.

30 The present invention makes it possible to reduce the amount of soluble diluent and binder in a chewable calcium tablet while sustaining the desirable chewability by the production of a highly porous granulate by fluid bed granulation using a calcium compound with a relatively high degree of crystallinity and with smooth faces to the crystals. This high degree 35 of porosity, desirably 20 to 30%, results in the final

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chewable tablet having improved sensoric properties despite having a high calcium content. Such properties include improved dispersion in water and reduced stickiness during mastication.

5        The porosity of the granulate or tablet may be determined using mercury intrusion porosimetry (e.g. using a Carlo Erba Porosimeter 2000), and by helium adsorption, e.g. using an AccuPyc 1330 pycnometer to measure true density and a Geopyc 1360 envelope 10 measuring apparatus. AccuPyc 1330 and Geopyc 1360 apparatus are available from Micrometrics. Mercury intrusion porosimetry is the more suitable of the two techniques for measuring the porosity of a granulate while both techniques can be used for measuring the 15 porosity of a tablet.

Viewed from a further aspect the invention provides a tablet (e.g. a lozenge, chewable tablet or a effervescent tablet) comprising a compressed granulate according to the invention and containing: calcium 20 carbonate; vitamin D<sub>3</sub>; a lubricant; citric acid; and an oligosaccharide; and, optionally but preferably, polyvinylpyrrolidone.

The invention will now be described further with reference to the following non-limiting Examples and the 25 accompanying drawings in which Figures 1 to 6 are scanning electron micrographs of six different grades of calcium carbonate and Figures 7A, 7B, 8A and 8B are scanning electron micrographs of granulates prepared according to the invention at lower (Figs. 7A and 8A) 30 and higher (Figs. 7B and 8B) magnification:

**EXAMPLE 1**

**Preparation of First Granulate**

35        A binder solution is prepared containing 27.7% by weight of polyvinylpyrrolidone (Kollidon K30) in purified water. This is temperature-controlled at 20°C

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or more preferably 25°C before spraying.

A batch of 74.5 parts by weight calcium carbonate (Scoralite 1B) and 23.3 parts by weight sorbitol (Neosorb P100T) is blended for two minutes using a high speed mixer (Fielder PMA 25/2G) set at maximum mixing speed. 5 3.0kg of this blend are then placed at 23-26°C in the mixer chamber of a Glatt GPCG3 fluid bed mixer.

The polyvinylpyrrolidone solution is then sprayed onto the fluidized blend at a rate of 40g/min until a 10 total of 280g of liquid has been added. Spraying is effected into air at an inlet temperature of 45°C and at ambient pressure.

Air at 70°C is then passed through the sprayed granulate until it is dry (about 0.2% by weight residual 15 moisture content). At this stage, the granulate temperature is about 44°C. The total duration of the spraying and drying stage is about 25 minutes.

At the end of the drying stage the first granulate has the following properties:

20 mean particle size and distribution  $D(v, 0.1) = 16 \mu\text{m}$ ,  $D(v, 0.5) = 100 \mu\text{m}$ , and  $D(v, 0.9) = 284 \mu\text{m}$

Bulk density: 0.73g/mL

Porosity: 20-30%

Flowability (Carrs index %) : 13

25 The mean particle size analysis is performed on a Malvern Mastersizer S long bench apparatus  $D(v, 0.1)$ ,  $D(v, 0.5)$ , and  $D(v, 0.9)$  give the particle sizes for which 10%, 50% and 90% of the particles by volume have sizes below the given values.

#### EXAMPLE 2

#### Preparation and Tableting of Second Granulate

35 4.4 parts by weight of sieved (< 60 mesh) Vitamin D<sub>3</sub> from Roche and 32 parts by weight of the first granulate are dry mixed in a twin cone convection blender to form a pre-mix.

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The pre-mix, the first granulate, lemon flavour granulate and aspartame are then dry mixed in a conical screw mixer to produce a granulate which is then mixed for 9 minutes. Magnesium stearate is added and mixed for an additional 3 minutes to produce a second granulate comprising:

5	Calcium carbonate	1250 parts by weight
	Sorbitol	390 parts by weight
	Polyvinylpyrrolidone	36.4 parts by weight
10	Vitamin D <sub>3</sub> 100 000 IU/g (100CWS from Roche)	4.4 parts by weight
	Lemon flavour (in dehydrated glucose syrup)	50.7 parts by weight
	Aspartame	1 part by weight
15	Magnesium stearate	6 part by weight

This mixture is then tabletted to produce biconvex tablets of 16mm diameter containing 1250 mg calcium carbonate.

The characteristics of the tablets are as follows:

20 **Breaking strength:** The chewable tablet has a normal biconvex shape and a diameter of 16 mm. The tablet initially has a breaking strength of 6 to 7.5 kp which can increase to approximately 8 to 9 kp after 24 hour storage. This breaking strength gives a satisfactory chewability and at the same time resistance towards handling and packaging into tablet bottles.

25 The initial breaking strength values may however vary between 4.5 to 8.0 kp according to the size of the tablet (12-21 mm).

30 **Friability:** A breaking strength of 6 to 7.5 kp for a chewable tablet with a diameter of 16mm results in friability values of less than 1%. This low value for the friability ensures sufficient firmness with respect to handling and packaging.

35 **Disintegration:** A characteristic feature of this chewable tablet formulation is the very fast disintegrating time.

- 15 -

The disintegration time is typically between 3 and 6 min. It is also a characteristic feature of the tablet that it disintegrates into the primary crystals of calcium carbonate which ensures a rapid exposure of calcium carbonate for dissolution.

This is important for the in vivo dissolution of calcium carbonate in the acidic gastric medium in the stomach and the subsequent absorption of calcium in the gastrointestinal tract.

10 **Porosity:** The tablet has a characteristic porosity of 25-30%. The porosity is determined by both mercury intrusion porosimetry and helium adsorption as described above. Both techniques gave porosity values in the range 25-30% for the tablet.

15 **Dissolution:** The dissolution rate is typically quick with 90% elemental calcium being dissolved within 10 min in 900 ml of 0.1 N HCl at 37°C (Ph. Eur., rotating paddle at 50 RPM).

20 **EXAMPLE 3**

**Lozenge to be sucked**

Using a process analogous to that of Examples 1 and 2 lozenges are prepared with the following composition:

25 **Calcium granulate:**

Calcium carbonate (Scoralite 1B):	1250 mg
Xylitol (CM50):	390 mg
Polyvinylpyrrolidone (Kollidon K 30):	36.40 mg

30 Vitamin D<sub>3</sub> 100 000 IU/g (100 CWS from Roche): 4.4 mg

Lemon flavor: 50.7 mg

Anhydrous citric acid: 8.0 mg

Aspartame: 1.0 mg

Magnesium stearate: 6.0 mg

35 Sum tablet weight:

1747 mg

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EXAMPLE 4

Sachet product to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 2 but with sorbitol replaced by anhydrous citric acid, 5 sachets are prepared with the following granulate contents:

Calcium granulate:

Calcium carbonate (Scoralite 1A): 1250 mg

Citric acid, anhydrous

(powder quality) 2150 mg

Polyvinylpyrrolidone (Kollidon VA 64 or 90F): 36.60 mg

Vitamin D<sub>3</sub> 100 000 IU/g (100 CWS from Roche): 4.4 mg

Lemon flavor: 300 mg

Aspartame: 15.0 mg

Acesulfam K: 14.0 mg

Sum sachet contents weight: 3770 mg

EXAMPLE 5

Granulate to be dispensed from a granulate dispensing unit

This product may be used as a food additive or as a functional food where the consumer takes a dosage equivalent to 500-1000 mg of elemental calcium and uses this as a supplement in daily food products, such as for example breakfast cereals and fruit juices. The 30 granulate is produced by a process analogous to that of Examples 1 and 2 with the following composition:

Calcium granulate:

Calcium carbonate (Scoralite 1A+1B): 1250 mg

Xylitol (CM 50): 390 mg

Polyvinylpyrrolidone (Kollidon VA 64): 36 mg

Granulate weight per 500 mg Ca<sup>2+</sup>: 1676 mg

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In this Example, polyvinylpyrrolidone may be replaced by inulin (e.g. Raftiline ST), 36.60 mg. Additional inulin or oligofructose may be added to bring the total oligosaccharide content to 1 to 5 g per dosage.

5

EXAMPLE 6

Effervescent tablet to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 10 2, effervescent tablets are prepared with the following composition:

Calcium granulate:

Calcium carbonate (Scoralite 1A+1B) : 1250 mg

15 Citric acid, anhydrous 2150 mg  
(powder quality)

Polyvinylpyrrolidone (Kollidon VA 64  
or 90F) : 36.60 mg

Vitamin D<sub>3</sub> 100 000 IU/g (100 CWS from Roche) : 4.4 mg

20 Lemon flavor: 300 mg

Aspartame: 15.0 mg

Acesulfam K: 15.0 mg

Sodium stearate fumarate: 19.0 mg

25 Sum tablet weight: 3790 mg

In this Example, aspartame and acesulfam K may be partially or totally replaced by inulin or oligofructose 30 with these providing 1 to 4 oligosaccharide per tablet.

EXAMPLE 7

Calcium carbonate grades

35 Samples of Scoralite 1B, Scoralite 1A, Super Purity CaCO<sub>3</sub>, Medicinal Heavy CaCO<sub>3</sub>, Pharmacarb LL and Merck 2064 were investigated using a scanning electron

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microscope (SEM). SEM pictures of these grades of calcium carbonate are presented in Figures 1 to 6 respectively of the accompanying drawings.

5      Granulates made analogously to Example 1 using Scoralite 1B and Super Purity CaCO<sub>3</sub> were also investigated by SEM and SEM pictures of these granulates at lower (A) and higher (B) magnifications are presented in Figures 7 and 8 of the accompanying drawings. The pictures of the two granulates clearly show their high 10 degree of porosity, a property which is important for the fast disintegration/dissolution of tablets made therefrom. Moreover, this high degree of porosity is important for the sensory properties such as chewability and avoidance of sticking to the teeth during 15 mastication.

#### EXAMPLES 8 TO 12

20      Analogously to Examples 1 and 2, chewable tablets and lozenges are prepared with the compositions set out in Table 1 below. The difference between a chewable tablet and a lozenge is simply in crushing strength or hardness, the lozenge being more forceably compressed so that it can be sucked and will last longer in the mouth.

25      The concentration of the binder in the aqueous granulation liquid and the granulation spray rate are adjusted in Examples 9 to 12 as follows:

Example 9: 20% maltodextrin solution, spray rate 31 g/min

30      Example 10: 15% inulin solution, spray rate 28 g/min.

Example 11: 15% inulin solution, spray rate 31 g/min.

Example 12: 28% PVP solution, spray rate 31 g/min.

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Example Number	8	9	10	11	12
Ingredients in calcium granulate					
5 CaCO <sub>3</sub> <sup>1</sup>	1250 mg				
Isoflavone extract <sup>2</sup>	-	-	-	-	62.5 mg
10 Xylitol <sup>3</sup>	390 mg	-	-	-	389 mg
Sucrose <sup>4</sup>	-	391 mg	-	-	-
15 Inulin <sup>5</sup>	-	-	390 mg	-	-
Isomalt <sup>6</sup>	-	-	-	390 mg	-
Polyvinyl-pyrrolidone VA64	36.40 mg	-	-	-	45.50 mg
15 Inulin <sup>5</sup>	-	-	24.00 mg	24.00 mg	-
Maltodextrin <sup>7</sup>	-	31.00 mg	-	-	-
Remaining Ingredients					
Vitamin D <sub>3</sub> <sup>8</sup>	4.4 mg				
20 Lemon Flavour	53.2 mg	52.6 mg	52.6 mg	52.6 mg	52.6 mg
Anhydrous Citric Acid	8.0 mg	-	-	-	-
Malic Acid	-	8.0 mg	8.0 mg	8.0 mg	8.0 mg
25 Aspartame	-	-	1.0 mg	1.0 mg	-
Magnesium Stearate	8.0 mg				
Tablet Weight	1750 mg	1745 mg	1738 mg	1738 mg	1820 mg

<sup>1</sup> Scoralite 1A + 1B<sup>5</sup> Raftiline ST<sup>2</sup> Novasoy 400<sup>6</sup> Isomalt PF<sup>3</sup> CM 50<sup>7</sup> Lycatab DSH<sup>4</sup> Tate & Lyle<sup>8</sup> 100 CWS

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In Examples 10 and 11, additional oligosaccharide (e.g. inulin or oligofructose) may be added to bring the oligosaccharide content to 1 to 5 g per dosage.

5

EXAMPLE 13

Calcium Carbonate Characteristics

Different samples (lots) of Scoralite 1B and Scoralite 1A + 1B were investigated for particle size (using 10 Malvern Particle size analysis performed on a Malvern Mastersizer S long bench apparatus and a Malvern Mastersizer 2000), specific surface area (BET analysis by nitrogen adsorption performed on a Sartorius micro balance) and apparent bulk density (using apparent bulk 15 density before settling (poured density) according to Ph. Eur., 3rd Edition, 1977). The values determined were as follows:

Scoralite Sample	1B	1B	1B	1A+1B	1A+1B	1A+1B
Apparent bulk density (g/mL)	1.09	1.04	1.02	0.95	0.99	0.89
D(v,0.5) $\mu$ m	15.1	14.7	15.9	13.3	13.7	11.8
D(v,0.1) $\mu$ m	8.8	8.7	8.1	6.3	6.5	3.9
D(v,0.9) $\mu$ m	24.3	23.4	27.8	23.5	24.2	23.0
Specific surface area (m <sup>2</sup> /g)	0.5	0.5	0.5	0.4	0.5	0.7

Claims:

1. A process for the preparation of an orally  
5 administrable calcium composition, said process  
comprising the steps of:

(i) obtaining a physiologically tolerable  
particulate calcium compound having a mean particle size  
in the range 3 to 40 $\mu$ m, having a crystalline structure  
and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g;

10 (ii) mixing said calcium compound with a water-  
soluble diluent and an aqueous solution of a water  
soluble binder in a fluid bed granulation apparatus and  
drying the resulting mixture to produce a first  
granulate;

15 (iii) optionally mixing said first granulate with  
one or more further components to produce a second  
granulate; and

(iv) optionally compressing said first or second  
granulate to form tablets.

20 2. A process as claimed in claim 1 wherein said  
calcium compound is selected from calcium carbonate,  
calcium lactate, calcium gluconate, calcium citrate,  
calcium glycerophosphate, calcium phosphate, calcium  
25 hydrogen phosphate, calcium glucuronate, calcium  
aspartate, calcium glucoheptonate and mixtures of two or  
more thereof.

30 3. A process as claimed in claim 1 wherein said  
calcium compound is calcium carbonate.

4. A process as claimed in any one of claims 1 to 3  
wherein said calcium compound makes up 68 to 80% wt. of  
said first granulate.

35 5. A process as claimed in any one of claims 1 to 4  
wherein said calcium compound makes up 60 to 95% wt. of

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said second granulate.

6. A process as claimed in any one of claims 1 to 5 wherein in step (i) the same material is used as said diluent and as said binder.

5 7. A process as claimed in any one of claims 1 to 6 wherein said water-soluble diluent comprises at least one sweetener.

10

8. A process as claimed in claim 7 wherein said sweetener is selected from sorbitol, xylitol, isomalt, mannitol, sucrose, fructose, maltodextrin, inulin and oligofructose.

15

9. A process as claimed in any one of claims 1 to 8 wherein said water-soluble diluent makes up 70 to 96% wt. of the total weight of said water-soluble diluent and said water-soluble binder in said first granulate.

20

10. A process as claimed in any one of claims 1 to 9 wherein said water-soluble binder is selected from celluloses, polysaccharides, maltodextrin, inulin and polyvinylpyrrolidone.

25

11. A process as claimed in any one of claims 1 to 10 wherein said water-soluble binder is a polyvinylpyrrolidone.

30

12. A process as claimed in any of claims 1 to 11 wherein said first granulate has a particle size distribution of  $D(V, 0.1) = 15-21 \mu\text{m}$ ,  $D(V, 0.5) = 70-120 \mu\text{m}$  and  $D(V, 0.9) = 190-330 \mu\text{m}$ .

35

13. A process as claimed in any one of claims 1 to 12 wherein a said further component is mixed with said first granulate, said further component being selected

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from: vitamin B<sub>6</sub>, vitamin K, vitamin C, vitamin D, isoflavones, inulin, and oligofructose and mixtures of two or more thereof.

5 14. A process as claimed in any one of claims 1 to 13 wherein in step (ii) said calcium compound is also mixed with isoflavones.

10 15. A granulate comprising a fluid bed granulation granulate product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g.

15 16. A granulate as claimed in claim 15 further comprising a lubricant.

20 17. A granulate as claimed in either of claims 15 and 16 wherein said calcium compound is selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate, calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof.

25 18. A granulate as claimed in any one of claims 15 to 17 said diluent is a sweetener selected from sorbitol, xylitol, mannitol, sucrose, fructose, maltodextrin, inulin and oligofructose.

30 19. A granulate as claimed in any one of claims 15 to 18 wherein said water-soluble binder is selected from celluloses, polysaccharides, maltodextrin, inulin and polyvinylpyrrolidone.

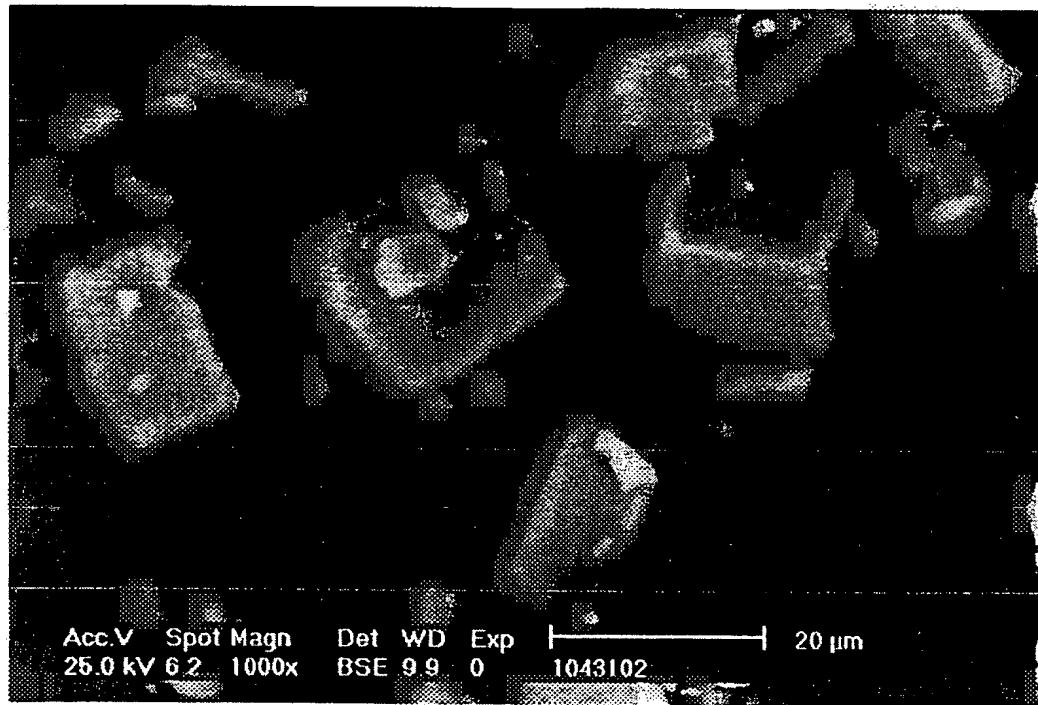
35 20. A granulate as claimed in any one of claims 15 to

- 24 -

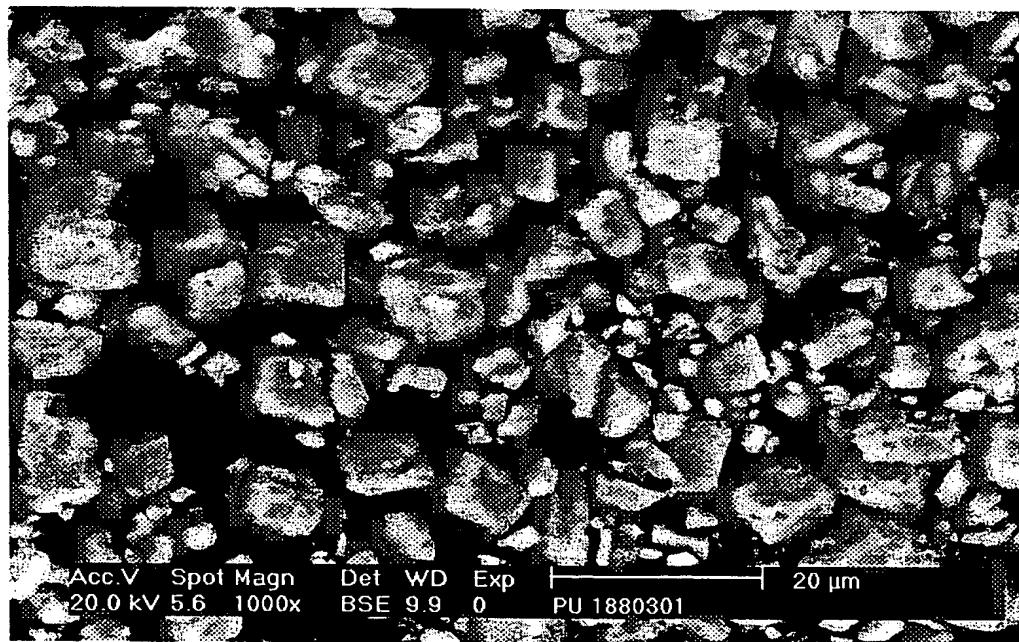
19 comprising a further component selected from: vitamin B<sub>6</sub>, vitamin K, vitamin C, vitamin D, isoflavones, inulin, and oligofructose and mixtures of two or more thereof.

5 21. A tablet comprising a compressed granulate as claimed in any one of claims 15 to 20 containing: calcium carbonate; vitamin D<sub>3</sub>; a lubricant; citric acid; and an oligosaccharide.

1 / 5



**FIG. 1**  
SCORALITE 1B



**FIG. 2**  
SCORALITE 1A

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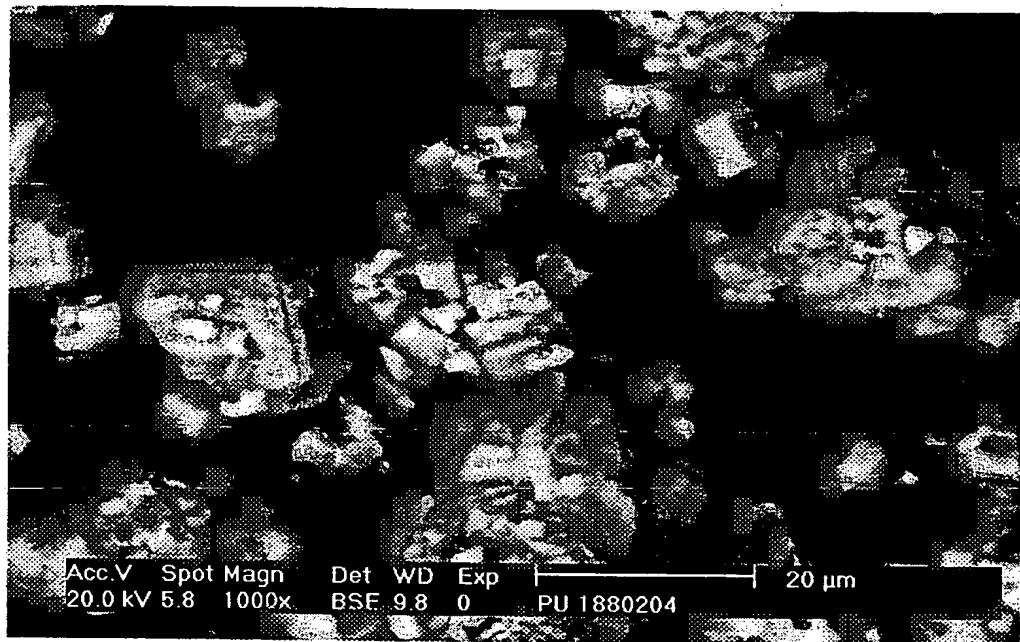


FIG. 3  
SUPER-PURITY CaCO<sub>3</sub>

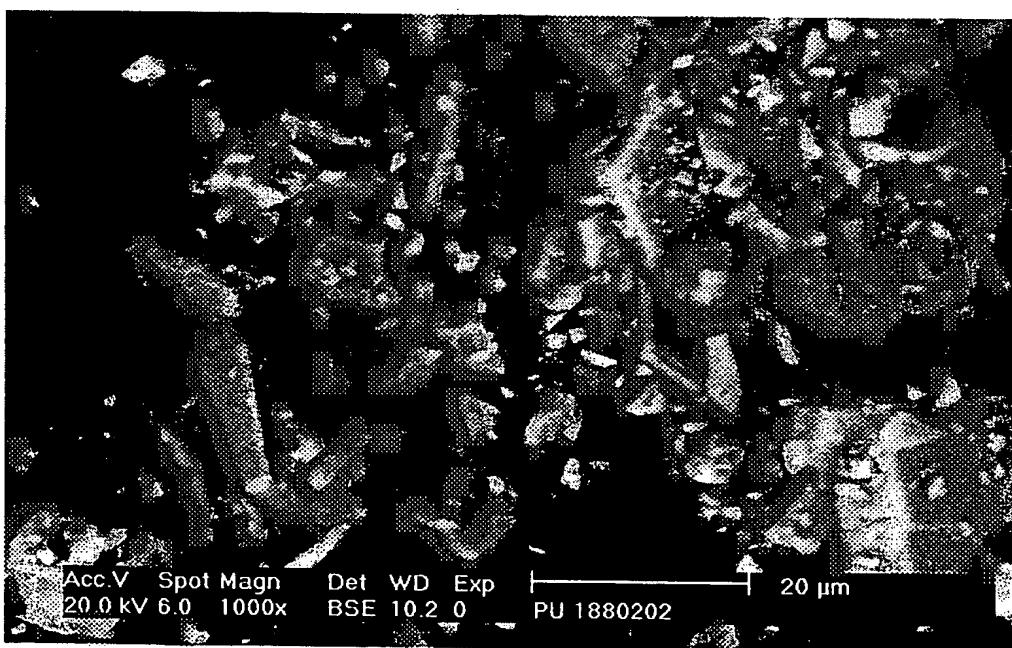
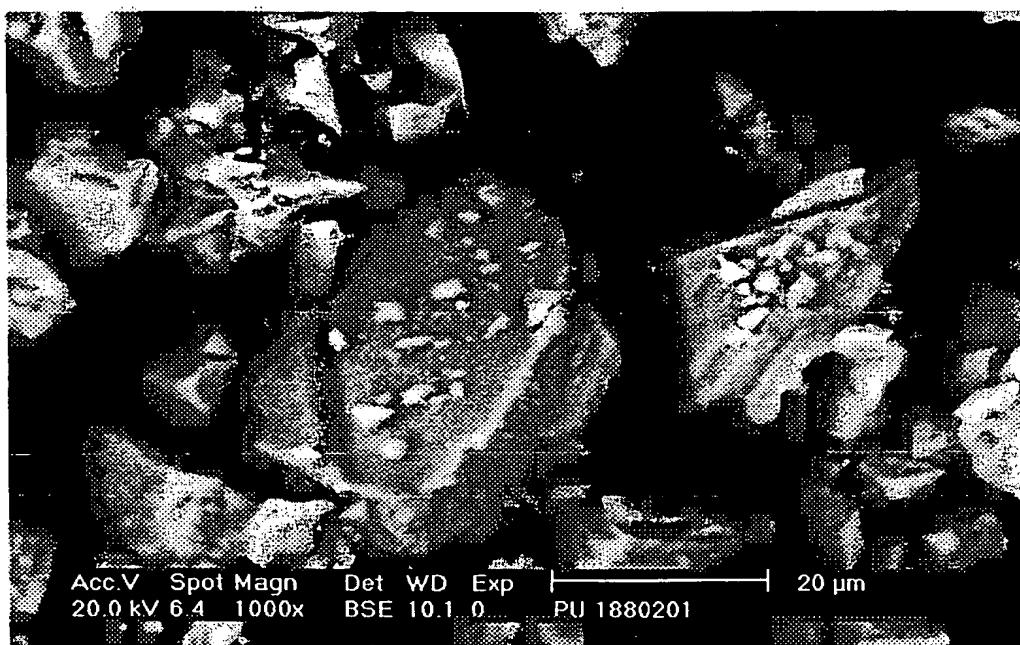
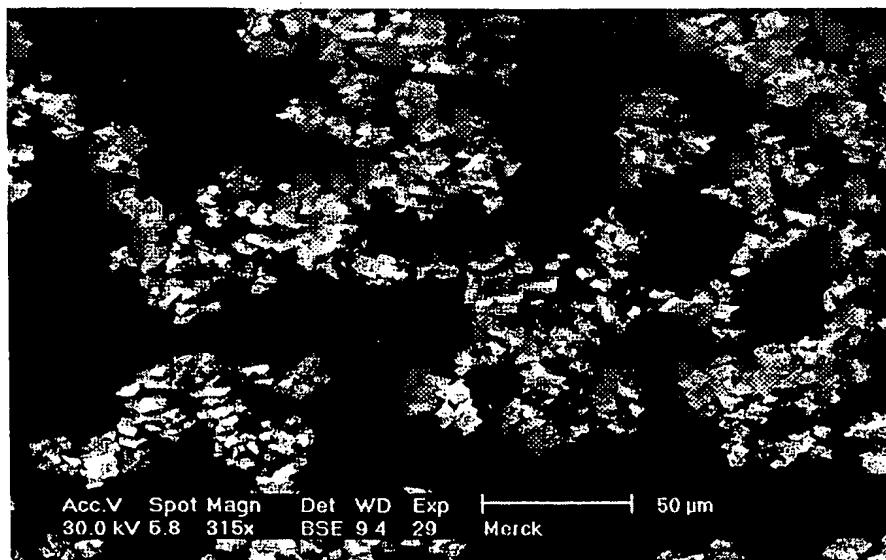


FIG. 4  
MEDICINAL HEAVY CaCO<sub>3</sub>

3 / 5

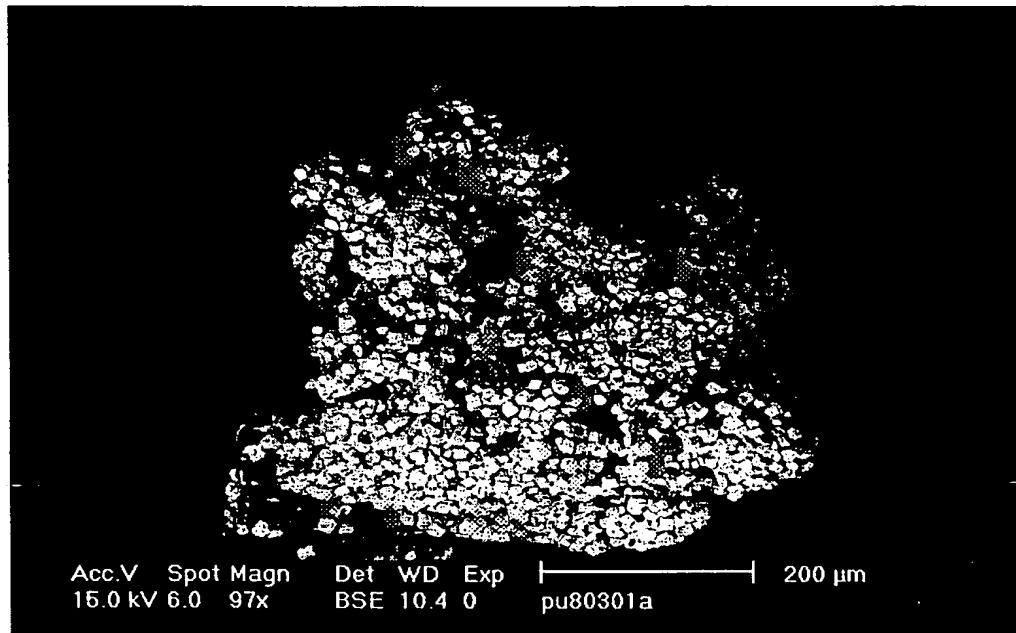


**FIG. 5**  
PHARMA CARB LL

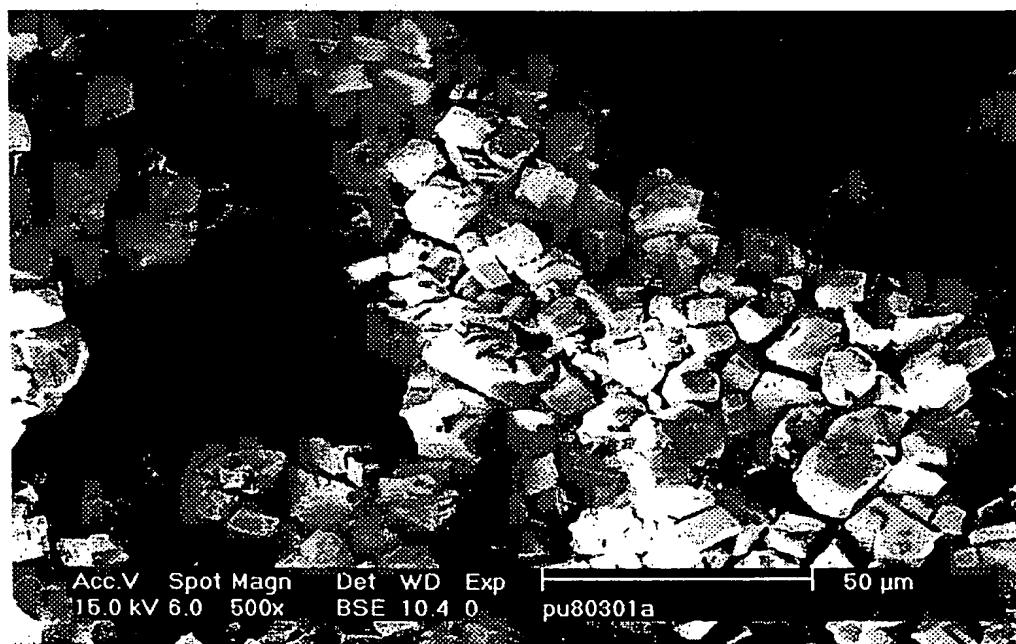


**FIG. 6**  
MERCK 2064

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**FIG. 7A**

SCORALITE 1B

**FIG. 7B**

SCORALITE 1B

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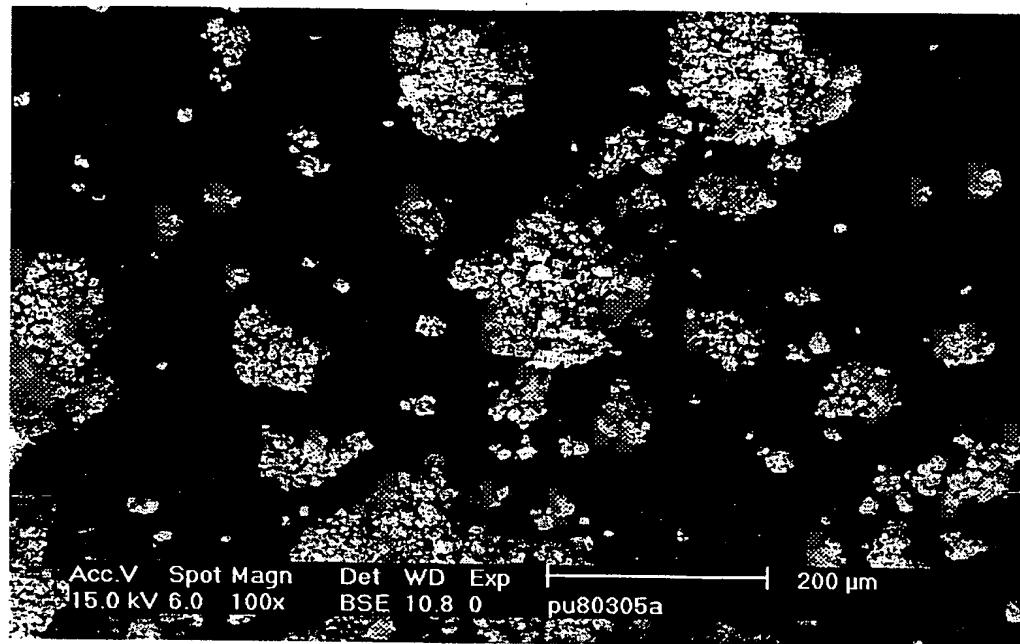


FIG. 8A

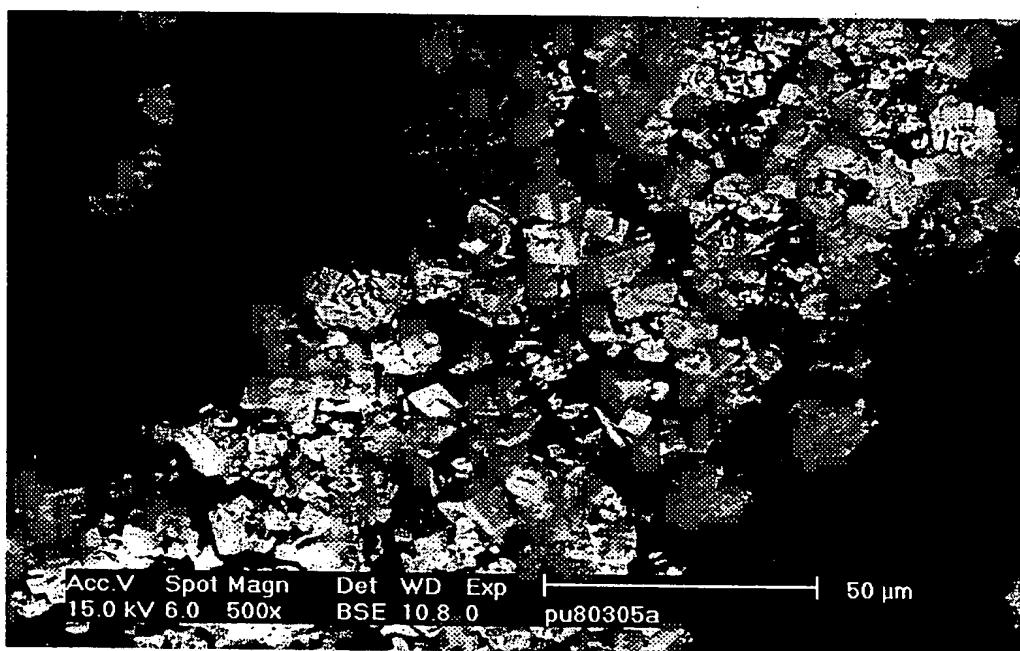
SUPER PURITY CaCO<sub>3</sub>

FIG. 8B

SUPER PURITY CaCO<sub>3</sub>

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03666

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 192 460 A (DYNAGRAN ) 27 August 1986 (1986-08-27)  claims 1-25 page 29; example 13 ---	1-4, 6-11, 15-18
Y	FR 2 724 844 A (LABORATOIRE INNOTHERA) 29 March 1996 (1996-03-29) claims 1-8 page 3; example 1 ---	1-21
Y	DE 196 17 487 A (MERCK) 6 November 1997 (1997-11-06) claims 1,2,5,7 page 3, line 43 - line 45 example 1 ---	1-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

<sup>o</sup> Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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Date of the actual completion of the international search

Date of mailing of the international search report

1 February 2000

10/02/2000

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/03666

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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		DE 69013689	T	02-03-1995	
		DK 487774	T	21-11-1994	
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JP 5032554	A 09-02-1993	JP 2702325	B	21-01-1998	

INTERNATIONALE ANMELDUNG VERÖFFENTLICH NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

<b>(51) Internationale Patentklassifikation<sup>6</sup>:</b> <b>A61K 9/14, 9/20, 9/00</b>		<b>A1</b>	<b>(11) Internationale Veröffentlichungsnummer:</b> <b>WO 97/41835</b> <b>(43) Internationales Veröffentlichungsdatum:</b> 13. November 1997 (13.11.97)
<b>(21) Internationales Aktenzeichen:</b> PCT/EP97/01781 <b>(22) Internationales Anmeldedatum:</b> 10. April 1997 (10.04.97)		<b>(81) Bestimmungsstaaten:</b> CA, CN, CZ, HU, JP, KR, LT, LV, RU, SG, SI, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
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<b>(54) Title:</b> IMPROVEMENT IN THE TASTE OF ACTIVE PHARMACEUTICAL INGREDIENTS			
<b>(54) Bezeichnung:</b> GESCHMACKSVERBESSERUNG VON ARZNEIMITTELWIRKSTOFFEN			
<b>(57) Abstract</b> The invention relates to a process for improving the taste of solid formulations containing one or more active ingredients.			
<b>(57) Zusammenfassung</b> Die Erfindung betrifft ein Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten.			

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## Geschmacksverbesserung von Arzneimittelwirkstoffen

5 Die Erfindung betrifft ein Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, wie z. b. von wirkstoff- oder mineralstoffhaltigen Tabletten, und zwar sowohl des eigentlichen Geschmacks selbst als auch des sensorischen Empfindens im Mund.

10 Polyole und Polyolmischungen werden in großem Umfang als nicht Karies hervorrufende Zusatzstoffe und Trägerstoffe unter anderem für pharmazeutisch Wirkstoffe, Kau- und Lutschtabletten und andere Produkte der Pharmaindustrie und als Komprimate in der Lebensmittelindustrie verwendet. Gewonnen werden Polyole in der Regel durch Hydrierung der ihnen zugrundeliegenden Zucker. In fester Form können sie sowohl durch Kristallisation als auch durch Sprühtrocknung erhalten werden. Der besondere Vorteil einiger Polyole liegt darin, daß sie auch zum direkten Verpressen ohne weitere Hilfs- und Zusatzstoffe geeignet sind.

15 Die bekannten Polyole, Mannit, Lactit, Isomalt und Xylit sind gering hygroskopisch, zeigen jedoch schlechtes Tablettierverhalten, was sich in geringer Tablettenhärte, Deckeln und hohem Abrieb der Tabletten bemerkbar macht. Grundsätzlich werden hohe Tablettenhärten angestrebt, da in festen Formulierungen Trägerstoffe häufig nur in geringen Mengen eingesetzt werden und Wirkstoffe die Tablettenhärten drastisch vermindern können, so daß eine gegebene Rezeptur nicht tablettierbar ist.

20 Während Lactit, Isomalt und Xylit in der Komprimatherstellung eher ungebräuchlich sind, wird Mannit in pharmazeutischen Formulierungen durchaus verwendet.

25 30 Der Einsatz von Mannit stellt jedoch einen erhöhten Arbeitsaufwand dar, da er in der Regel vor dem Verpressen mit den übrigen Bestandteilen der Rezeptur naßgranuliert werden muß. Erhältlich ist im Handel auch direkt tablettierbarer Mannit, mit dem sich jedoch nur unbefriedigende Härten erzielen lassen, verglichen mit denen bei Verwendung von Sorbit.

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5 Mit Sorbit, insbesondere durch Sprührocknung hergestellt, werden sehr gute Tablettenhärten erhalten. Gleichzeitig weisen die hergestellten Komprimeate besonders glatte Oberflächen auf. Aus einer Veröffentlichung von Basedow et. al. ist bekannt, daß Calciumcarbonat-haltige Tabletten durch Verpressen mit sprühgetrocknetem oder kristallinem Sorbit hergestellt werden können. Jedoch ist die Hygroskopizität von Sorbit höher als die anderer Polyole. Dadurch ist seine Verwendbarkeit eingeschränkt. Auch ist in diesem Zusammenhang kein Hinweis in der Literatur zu finden, daß durch Sorbit oder  
10 ein anderes Polyol das Geschmacksbild einer Formulierung wesentlich verbessert werden könnte.

15 Bei der Formulierung oral zu verabreichender pharmazeutischer Zusammensetzungen bereitet in vielen Fällen nicht nur bei flüssigen Applikationsformen das vom Verwender empfundene Geschmacksbild Probleme. Insbesondere beim Kauen von Antacidum-Tabletten wird ein kreidiger Geschmack als unangenehm empfunden. Es wurde bislang wenig erfolgreich durch verschiedenste Zusatzstoffe versucht, diesen kreidigen Geschmack zu überdecken. Bekannte Antacida wiederum vermitteln im Mund einen unerwünschten kreidigen, seifigen Geschmack, der durch herkömmliche Zusatzstoffe nur schwach gemildert werden kann, jedoch beim Kauen weitgehend wieder auftritt.

20 25 Als problematisch hat sich auch bei verschiedensten Wirkstoffen ein als äußerst bitter empfundener Geschmack erwiesen. Eine Maskierung besonders bitterer oder kreidiger Wirkstoffe ist bisher auch durch den Zusatz von Geschmacks- oder Aromastoffen nicht gelungen. Es besteht zwar die Möglichkeit, entsprechende Wirkstoffe enthaltende Tabletten mit einem Überzug zu versehen, diese Methode ist jedoch ungeeignet, wenn eine schnelle Aufnahme des Wirkstoffs, die bereits beim Kauen der Tabletten über die Mundschleimhaut erfolgt, angestrebt wird.

30 35 Besondere Anforderungen werden auch an die Oberfläche von Tabletten gestellt, die gelutscht werden sollen, wie beispielsweise Halstabletten. Erwünscht ist hierbei eine glatte Oberfläche der eigentlichen Tablette, die während des Lutschens erhalten bleibt und sich nicht nach und nach aufrauht.

5 Weiterhin werden heute im Bereich der Nahrungsergänzung (Vitamin- und Mineralstoffsupplementierung) vermehrt Lutsch- und vor allem Kautabletten angeboten. Insbesondere bei Tabletten zur Mineralstoffanreicherung ist der Trägeranteil sehr gering, so daß das Geschmacksbild weitgehend vom entsprechenden Mineralstoff geprägt ist.

10 Des weiteren versucht man, bei der Herstellung von festen Formulierungen zunehmend direkt verpreßbare Wirkstoffe (DC-Wirkstoffe) einzusetzen, um Produktionskosten zu senken.

15 Aufgabe dieser Erfindung ist es daher, ein Verfahren zur Verfügung zu stellen, wodurch einerseits das Geschmacksbild von festen Formulierungen verbessert wird, gleichzeitig aber auch das sensorische Mundgefühl der hergestellten Produkte vorteilhaft beeinflußt wird.

20 20 Es wurde nun gefunden, daß das Geschmacksbild von festen Formulierungen verbessert werden kann, indem eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, durch Verpressen in einer festen Darreichungsform hergestellt wird.

25 25 Gegenstand der Erfindung ist somit ein Verfahren zur Herstellung von DC-Wirkstoffen, die zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten, beitragen, dadurch gekennzeichnet, daß man eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtrocknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, durch Verpressen in einer festen Darreichungsform herstellt. Die eingesetzte Gesamtmenge Polyol ist dabei so zu wählen, daß in dem nach dem erfindungsgemäßen Verfahren hergestellten 30 30 pulverförmige Substanzgemisch 10 bis 90 Gew.-%, insbesondere 25 bis 75 Gew.-% enthalten sind.

35 35 Die erfindungswesentliche Zusammensetzung ist dabei erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Versprühen des erhaltenen wässrigen Gemischs in einem Luft-

strom mit einer Temperatur von 120 bis 300 °C, vorzugsweise 140 bis 190 °C. Es ist aber auch möglich das erhaltene wäßrige Gemisch in einem Luftstrom mit einer Temperatur von 40 bis 120 °C zu verwirbeln.

5 Dem wäßrigen Gemisch können vor der Co-Sprühtrocknung oder Wirbelschichtgranulation geschmackskorrigierende Substanzen und gegebenenfalls Farbstoffe hinzugefügt sein. Als geschmackskorrigierende Substanzen kommen u. a. natürliche oder synthetische Süßstoffe aus der Gruppe Saccharin, Aspartam®, Acesulfam K, Neoheperidin DC, Sucralose, Thaumatin oder Steviosid in Frage. Als Polyole sind solche aus der Gruppe Sorbit, Mannit, Lactit, Isomalt, Maltit Erythrit oder Xylit einsetzbar. Diese können in einer Menge von 10 bis 10 90 Gew.-%, insbesondere 25 bis 75 Gew.-% im hergestellten Produkt enthalten sein.

15 Gegenstand der Erfindung sind somit auch die durch das erfindungsgemäße Verfahren hergestellten festen Formulierungen mit verbessertem Geschmacksbild. In diesen Formulierungen können einerseits Mineralstoffe aus der Gruppe physiologisch verträglicher Ca-, Mg-, Na-, K-, Fe- und Zn-Salze in einer Menge von 0,1 bis 90 Gew.-%, insbesondere von 25 bis 75 Gew.-%, gegebenenfalls Spurenelemente, sowie ein oder mehrere Vitamin(e) und gegebenenfalls ein oder mehrere eventuell bitter schmeckende Wirkstoffe enthalten sein.

20 In den nach dem erfindungsgemäßen Verfahren hergestellten Formulierungen können ein oder mehrere pharmazeutische Wirkstoffe enthalten sein. Solche Wirkstoffe können unter anderem sein Antacida, Antiallergika, Analgetika, Hormone, Steroide, Östrogene, Kontrazeptiva, nasale Dekongestionsmittel, H<sub>1</sub>- und H<sub>2</sub>-Antagonisten, β<sub>2</sub>-Stimulatien, Vasodilatoren, Antihypertensiva, infektionsvorbeugende 25 Mittel, Laxantien, Antitussiva, Bronchodilatoren, Mittel gegen Hals- schmerzen, Wismut und seine Salze, Pilzmittel, Antibiotika, Stimulanzien (wie z. B. Amphetamine) Alkaloide, orale Hypoglycaemica, Diuretica, Cholesterin senkende Mittel, Kombinationen verschiedener pharmazeutisch wirksamer Mittel oder andere. Diese Wirkstoffe können 30 in einer Menge von 0,1 bis 70 Gew.-% enthalten sein.

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5 Die Wirkstoffe können als beschichtete Teilchen, Liposomen oder Mikropartikel vorliegen. Als Beschichtung können übliche, in der Pharmazie verwendete Substanzen dienen. Die Teilchengröße der Wirkstoffe beträgt vorzugsweise 0,1 bis 800 µm mit einer Schüttdichte von 0,15 bis 1 g/cm<sup>3</sup>.

10 Natürlich sind die im vorhergehenden Text gegebenen Gew.-%Angaben so zu verstehen, daß die Wahl der Gewichtsprozente der eingesetzten Substanzen in der Summe 100 nicht übersteigen.

15 Der Begriff Polyol steht für Zuckeralkohole der allgemeinen Formel CH<sub>2</sub>OH-(CHOH)<sub>n</sub>-CH<sub>2</sub>OH, wobei n für 2 bis 6, vorzugsweise 3 bis 4, steht, sowie deren dimere Anhydride, insbesondere C<sub>12</sub>H<sub>24</sub>O<sub>11</sub>.

20 20 Insbesondere steht der Begriff Polyole für Hexite wie Sorbit und Mannit, Pentite wie Xylit, möglich sind aber auch C<sub>4</sub>-Polyalkohole wie Erythrit oder C<sub>12</sub>-Polyalkohole wie Lactit oder Maltit. Der Begriff Polyole steht aber auch für geeignete Kohlehydrate.

25 25 Zur Sprühtrocknung wird eine wässrige Lösung von mindestens einem Polyol verwendet. Der Feststoffgehalt wird zuvor vorzugsweise durch Mischen bei einer Temperatur von bis 80 °C mindestens einer Polyol-Lösung mit einer oder mehrerer Lösungen oder Suspensionen des oder der gewünschten Wirkstoffe im gewünschten Verhältnis auf etwa 10 - 90 Gew.-%, insbesondere 50 bis 72 Gew.-% eingestellt.

30 30 Die Versprühung wird durch Zerstäuben mittels Düsen, vorzugsweise mittels eines Zentrifugalzerstäubers, in einem auf eine Temperatur von 120 bis 300 °C, vorzugsweise 140 bis 190 °C erwärmten, trockenen, zentrifugal eingeblasenen Luftstrom durchgeführt. Die Menge der zugeführten Polyollösung und der eingeblasenen Heißluft wird so abgestimmt, daß das erhaltene pulverförmige Substanzgemisch bis auf einen Wassergehalt von etwa 0,1 bis etwa 1 Gew.-%, gegebenenfalls im Fließbett, getrocknet wird. Auf jeden Fall sollte der Wassergehalt unterhalb 1 Gew.-% liegen.

Die Wirbelschichtgranulation wird, wie z. B. in P. Grassmann, F. Widmer „Einführung in die thermische Verfahrenstechnik“ beschrieben, durchgeführt.

5 Aufgrund der besonderen Herstellungsart durch Versprühen einer wässrigen Lösung ist es möglich, nicht wasserlösliche und wasserlösliche Zusätze, wie z. b. Zitronensäure, Süßstoffe, insbesondere Ace-sulfam K, Aspartam®, Saccharin, Cyclamat, Sucratose, Neohesperidin DC, Farbstoffe sowie pharmazeutische Wirkstoffe, wie z. B. Analgetika, Antacida und dergleichen, Vitamine und gegebenenfalls Spurenelemente homogen in den erfindungsgemäßen Zusammensetzungen, bzw. festen Formulierung und den daraus hergestellten Tabletten zu verteilen.

10 Die gegebenenfalls zuzusetzenden Bindemittel sind dem Fachmann geläufig und dienen der Erhöhung der Festigkeit der Zusammensetzung. Als Bindemittel bevorzugt sind Cellulose-Derivate, insbesondere Hydroxypropylmethylcellulose, Carboxymethylcellulose oder Stärke.

15 Die so charakterisierten Polyol-Zusammensetzungen besitzen eine Reihe von vorteilhaften Tablettiereigenschaften:

20 Überraschenderweise kann festgestellt werden, daß durch das erfindungsgemäße Verfahren unter Verwendung der erfindungsgemäßen Zusammensetzungen feste Formulierungen, insbesondere Tabletten, mit einem erheblich verbesserten Geschmacksbild und sensorischem Mundgefühl erhalten werden. Gleichzeitig sind diese vorteilhaften Eigenschaften mit der Möglichkeit verbunden, die durch Co-Sprühtröcknung bzw. Wirbelschichtgranulation erhaltenen Zusammensetzungen direkt zu verpressen. Es handelt sich dabei also um direkt verpreßbare Wirkstoffformulierungen (DC-Wirkstoffe).

25 Bei Verwendung von Formulierungen mit einem hohen Mineralstoffgehalt von bis zu 90 Gew.-% werden einerseits drastisch verbesserte Tablettiereigenschaften gefunden, andererseits sind die hergestellten Tabletten während des Verpackungsvorgangs durch einen wesentlich geringeren Abrieb gekennzeichnet. Auch werden bei Verwendung der erfindungsgemäßen Zusammensetzungen bei gleicher Preßkraft, wie

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5 sie bei bekannten polyolhaltigen Formulierungen angelegt wird, härtere Tabletten mit glatteren Oberflächen erhalten. Dieses anfänglich empfundene verbesserte sensorische Gefühl im Mund wird auch  
10 beim Kauen oder Lutschen empfunden, da der sonst übliche kreidige, oder gegebenenfalls seifige Geschmack weitestgehend überdeckt ist. Überraschender Weise wird jedoch nicht nur das Geschmacksbild dieser Mineralstofftabletten verbessert. Auch Formulierungen, in die äußerst bitter schmeckende Wirkstoffe eingearbeitet sind, werden als wesentlich wohlschmeckender empfunden, da der Bittergeschmack nicht mehr so extrem durchschlägt.

15 Die nachfolgenden Beispiele dienen der besseren Veranschaulichung der beschriebenen und beanspruchten Erfindung, sind jedoch nicht zur Einengung des Schutzbereichs auf diese Beispiele geeignet.

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**B e i s p i l e****Beispiel 1****Antacidum-Tablette****5      Zusammensetzung der Tablettiermischung:**

10	Calciumcarbonat	65,50 %
	Karion Instant	28,19 %
	Karion Pulver P300	4,70 %
	Chlorophyllin 100 %	0,01 %
15	Neohesperidin DC	0,10 %
	Pfefferminzaroma Naefco (Fa. Firmenich)	0,30 %
	Mg-Stearat	1,00 %

**15      Mechanische Herstellung der Mischung:**

Calciumcarbonat und Sorbit (Karion Instant und Karion Pulver P300) werden in einem Turbulamischer 5 Minuten gemischt. Anschließend wird Chlorophyllin, Neohesperidin DC und das Pfefferminzaroma zugegeben und weitere 5 Minuten gemischt. Die Mischung wird durch ein Sieb mit einer Porenweite von 1 mm gegeben. Über die gesiebte Mischung wird Magnesiumstearat durch ein Sieb, das eine Porenweite von 250 µm aufweist, aufgesiebt und erneut 5 Minuten gemischt. Die so erhaltene Mischung wird tablettiert.

**25      Herstellung der Mischung durch Co-Versprühen:**

Calciumcarbonat, Sorbit, Neohesperidin DC und Chlorophyllin werden in der vorher genannten Weise cugesprührt. Das cugesprühte Material und das Aroma werden im Turbulamischer vorgelegt, Magnesiumstearat über ein Sieb, das eine Porenweite von 250 µm aufweist, aufgesiebt und 5 Minuten gemischt. Die so erhaltene Mischung wird tablettiert.

Ergebnisse:

		Mechan. Mischung	Cogesprühtes Material
5	Tablettierung (qualitativ)	Mischung rieselt sehr schlecht, Matritzenfüllung nicht immer vollständig, Deckeln der Tabletten	einwandfreie Tablettierung
10	Fließneigungswinkel	37,5°	32,6°
	Tablettenhärte	40 N bei 19 KN (max. erzielbare Tablettenhärte)	129 N bei ca. 8 KN
15	S <sub>rel.</sub> Tablettengewicht	nicht auswertbar	0,19 %
	Abrieb (Roche)	nicht auswertbar	0,37 %
20	Sensorik	stark kreidiger Geschmack, Mundgefühl stark kreidig, sehr stumpf, Aroma wenig ausgeprägt, da vom kreidigen Geschmack maskiert	gut kaubare Tabletten ohne kreidiges Mundgefühl, Geschmack nur sehr schwach kreidig, Aroma gut erkennbar
25	Wirkstoff-Verteilung		
	Mittelwert (in % vom theoret. Wert)	98,2	99,9
30	Abweichung (min/max)	96,0 - 99,8	99,6 - 100,2
	Abweichung	3,8 %	0,6 %

**Beispiel 2****Analgetikum-Tablette****Zusammensetzung des Tablettiermaterials:**

5	Acetylsalicylsäure (ASS)	74,0 %
	Sorbit-Anteil	24,5 %
(Instant-Qualität beigemischt, bzw. mit ASS gesprührt)		
	Acesulfam K	0,5 %
	Magnesiumstearat	1,0 %

**Tablettier- und Geschmacksvergleich****Herstellung einer mechanischen Mischung:**

ASS wird durch Mahlung fein gepulvert und mit Sorbit Instant im Turbula-Schüttel-Mischer einschließlich des mikronisierten Süßstoffes ASK verrieben. Anschließend erfolgt eine Siebung zur Desagglomeration mit einem 1 mm-Sieb und die Nachmischung mit Magnesiumstearat und anschließend die Tablettierung.

**Herstellung von co-gesprühtem Tabletten Material:**

20 Feingepulverte, gemahlene ASS wird teilweise (ca. 5 %) in der Wirbelschicht vorgelegt, und der Rest im Verhältnis von ca. 1 : 1 in Sorbitlösung dispergiert. Die Dispersion wird durch Rühren aufrecht erhalten und mit dem Süßstoff ASK direkt in das Wirbelbett gesprührt, bei gleichzeitiger Wasserverdampfung.

25 Dem so gebildeten relativ feinen Sprühgranulat wird als Gleitmittel 1 % Magnesiumstearat beigemischt. Die erhaltene Mischung wird direkt tablettiert.

Ergbnisse:

		Mechan. Mischung	Cogesprühtes Material
5	Aussehen	wenig rieselfähige Mischung, deren beiden Hauptkomponenten erkennbar sind	homogenes, gut rieselfähiges Tablettier-Granulat
10	Tablettierung: 500 mg Preßkraft 10 kN		
15	Tablettenhärte:	90 N	210 N
20	Abrieb (Friab.)	0,6 %	0,3 %
	Sensorik	säuredominanter Geschmack, hohe Oberflächenrauheit der Tablette	gemilderter süßsaurer Geschmack, angenehmes Kauverhalten (glatte, wenig saugfähige Oberfläche)

**Beispiel 3**Vitamin C-Tablette

25	Ascorbinsäure	87,7 %
	Sorbit	10,0 %
	Orangenaroma (pulverförmig)	0,7 %
	Acesulfam K	0,6 %
30	Mg-Stearat	1,0 %

**Herstellung einer mechanischen Mischung:**

Die feinkristalline Ascorbinsäure wird im Turbula-Schüttelmischer mit Sorbit Instant (Körnung unter 0,3 mm), Süßstoff und Aroma innig verrieben. Danach wird das Gleitmittel Magnesium-Stearat aufgesiebt und eingemischt.

Herstellung von co-g sprühtem Tablettiermaterial:

Ascorbinsäure, Sorbit und Süßstoff werden mit ca. 40 % Feststoffanteil in Wasser bei 40 °C gelöst und auf ein gleichermaßen zusammengesetztes Bett von Kristallkeimen (Anteil an der Gesamtmasse ca. 15 %) im Wirbelgerät aufgesprührt. Das Sprühgranulat wird vor der Tablettierung mit dem gleichen Aroma und Magnesium-Stearat vermischt.

Ergebnisse:

	Mechan. Mischung	Cogesprühtes Material
10		
15	Aussehen Sorbitpartikel sind vereinzelt erkennbar	homogenes, gut rießfähiges Tablettiergranulat
20	Tablettierung: Menge: 500 mg Preßkraft 20 kN	
25	Tablettenhärte: 20 N	160 N
	Abrieb (Friab.): 22 %	0,2 %
30	Sensorik zu weiche Tabletten, rauhe Oberfläche, (nicht akzeptables Ergebnis)	süßsaure Vitamin C-Tablette mit glatter Oberfläche und angenehmen Kau-eigenschaften

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### Patentansprüche

1. Verfahren zur Verbesserung des Geschmacksbildes von festen Formulierungen, welche einen oder mehrere Wirkstoffe enthalten, dadurch gekennzeichnet, daß man eine einen oder mehrere Wirkstoffe enthaltende Zusammensetzung, erhältlich durch Co-Sprühtröcknung bzw. Wirbelschichtgranulation mit mindestens einem Polyol, bzw. Kohlehydrat durch Verpressen in einer festen Darreichungsform herstellt.
- 10 2. Verfahren gemäß Anspruch 1 dadurch gekennzeichnet, daß es sich bei den durch Co-Sprühtröcknung bzw. Wirbelschichtgranulation erhaltenen Zusammensetzungen um direkt verpreßbare Wirkstoffformulierungen handelt.
- 15 3. Verfahren nach den Ansprüchen 1 - 2 dadurch gekennzeichnet, daß man eine Zusammensetzung verwendet, welche geschmackskorrigierende Substanzen und gegebenenfalls Farbstoffe enthält.
- 20 4. Zusammensetzung nach den Ansprüchen 1 - 3, erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Versprühen des erhaltenen wässrigen Gemisches in einem Luftstrom mit einer Temperatur von 120 bis 300 °C, insbesondere 140 bis 190 °C.
- 25 5. Zusammensetzung nach den Ansprüchen 1 - 4, erhältlich durch Lösen von mindestens einem Polyol in Wasser und Lösen oder Suspendieren mindestens eines Wirkstoffs in einem Lösungsmittel und Verwirbelung des erhaltenen wässrigen Gemisches in einem Luftstrom mit einer Temperatur von 40 bis 120 °C.
- 30 6. Zusammensetzung nach einem oder mehreren der Ansprüche 1 - 5, dadurch gekennzeichnet, daß sie mindestens
  - a) einen Wirkstoff,
  - b) ein Polyol,
  - c) gegebenenfalls einen natürlichen oder synthetischen Süßstoff und
  - 35 gegebenenfalls einen Farbstoff enthält.

7. Zusammensetzung nach Anspruch 6, dadurch gekennzeichnet, daß sie einen Süßstoff aus der Gruppe Saccharin, Aspartam®, Acesulfam K, Neohesperidin DC, Sucratose, Thaumatin oder Steviosid enthält.
- 5 8. Zusammensetzung nach einem oder mehreren der Ansprüche 1 - 7, dadurch gekennzeichnet, daß sie mindestens einen oder mehrere Polyol(e) aus der Gruppe Sorbit, Mannit, Lactit, Isomait, Maltit, Erythrit oder Xylit enthält.
- 10 9. Feste Formulierung mit verbessertem Geschmacksbild, hergestellt nach einem Verfahren gemäß der Ansprüche 1 - 3.
- 10 10. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin 10 bis 90 Gew.-%, insbesondere 25 bis 75 Gew.-%, Mineralstoffe aus der Gruppe physiologisch verträglicher Ca-, Mg-, Na-, K-, Fe- und Zn-Salze, gegebenenfalls Spurenelemente und gegebenenfalls ein oder mehrere Vitamine, sowie und gegebenenfalls ein oder mehrere eventuell bitter schmeckende Wirkstoffe enthalten sind.
- 20 11. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin ein oder mehrere Wirkstoffe aus der Gruppe Analgetika, Antacida, Antiallergika, Hormone, Steroide, Östrogene, Kontrazeptiva, nasale Dekongestionsmittel, H<sub>1</sub>- und H<sub>2</sub>-Antagonisten, β<sub>2</sub>-Stimulatoren, Vasodilatoren, Antihypertensiva, infektionsvorbeugende Mittel, Laxantien, Antitussiva, Bronchodilatoren, Mittel gegen Halsschmerzen, Wismut und seine Salze, Pilzmittel, Antibiotika, Alkaloide, orale Hypoglycaemica, Diuretica, Cholesterin senkende Mittel enthalten sind.
- 25 12. Feste Formulierung gemäß Anspruch 9, dadurch gekennzeichnet, daß darin ein oder mehrere pharmazeutische Wirkstoffe in einer Menge von 0,1 bis 70 Gew-% enthalten sind.

Presskraft-Härteprofil

Diagramm 5

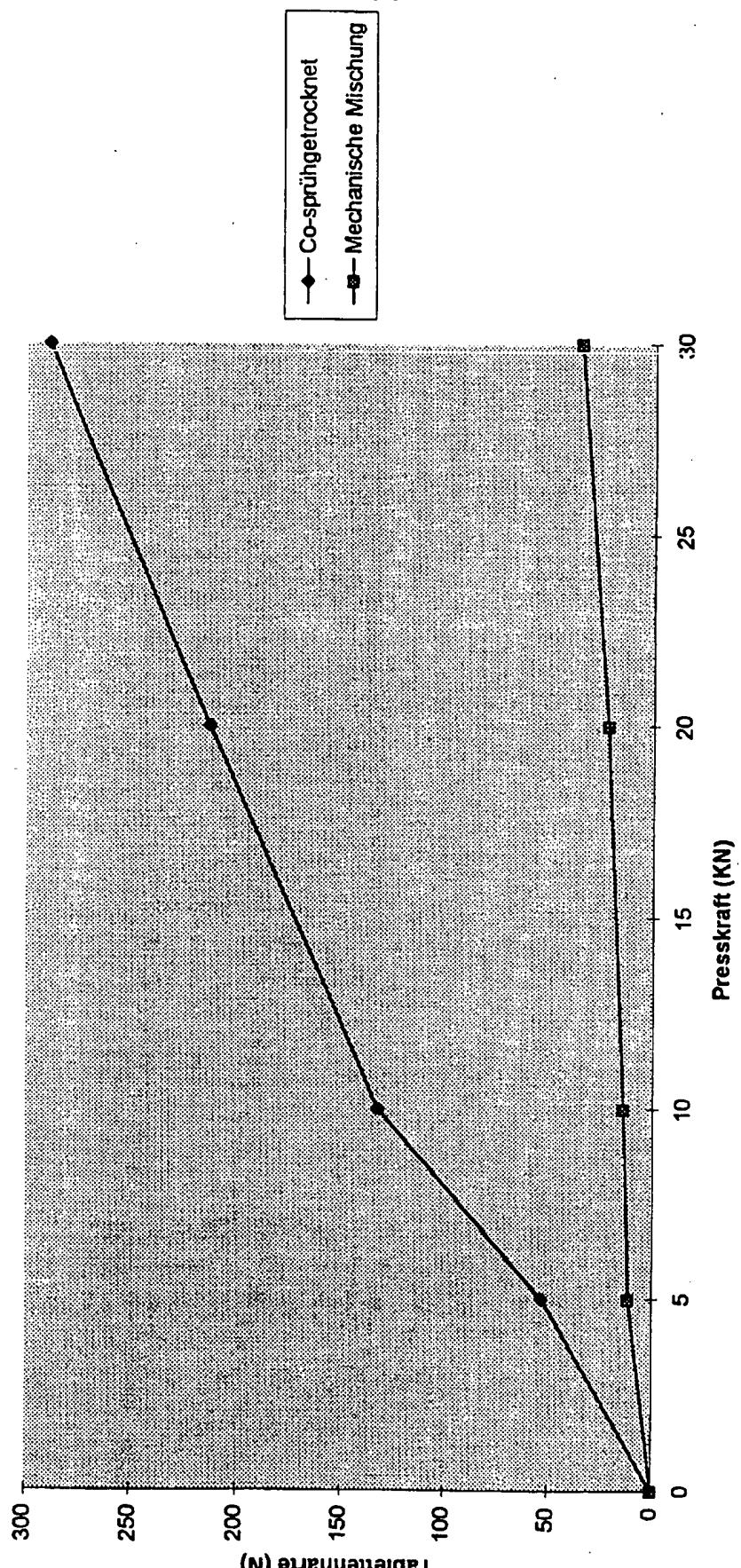


FIG. 1

Abrieb

Diagramm 7

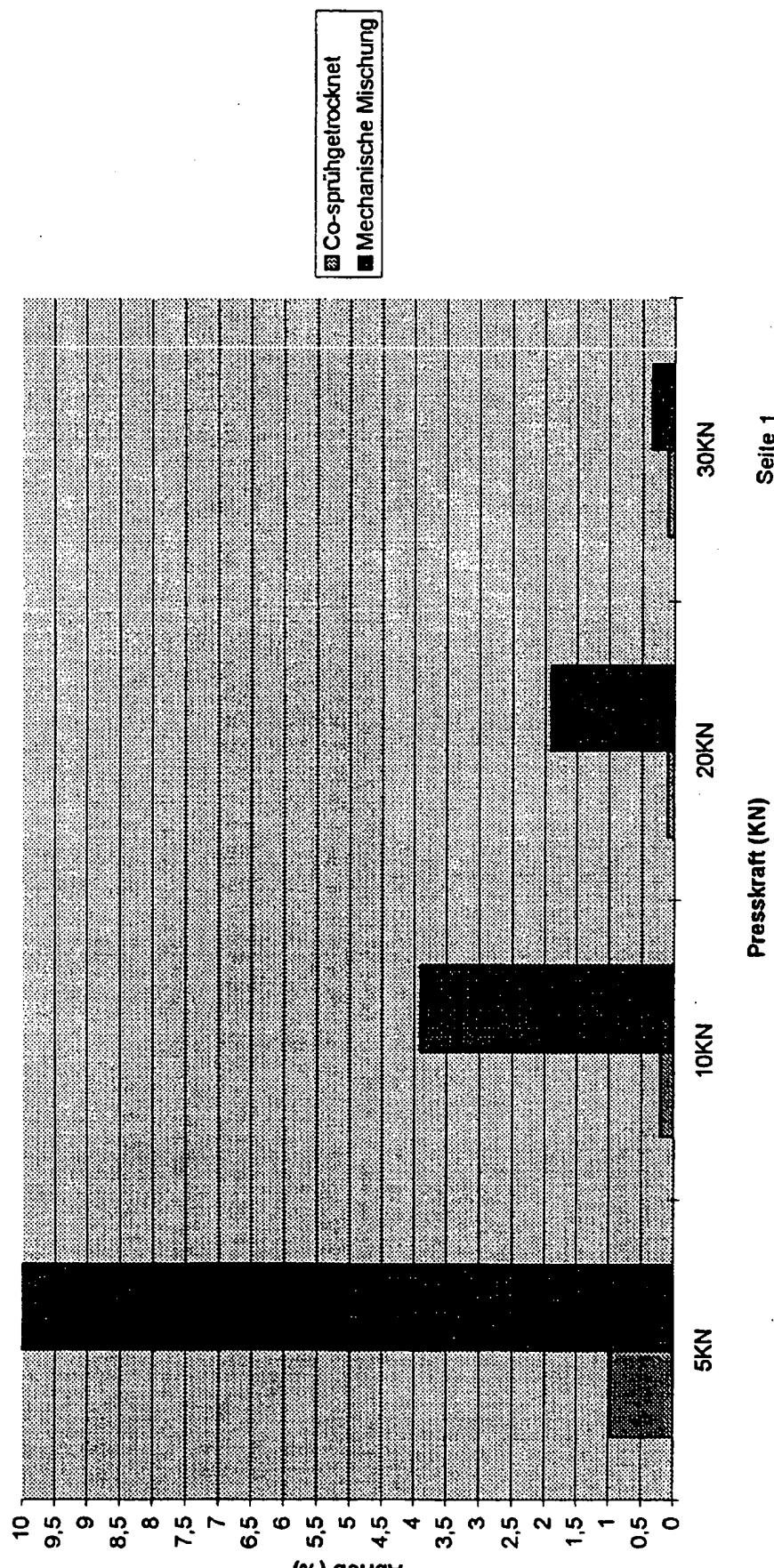


FIG. 2

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/01781

**A. CLASSIFICATION F SUBJECT MATTER**  
 IPC 6 A61K9/14 A61K9/20 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 143 576 A (WARNER LAMBERT) 5 June 1985</p> <p>see claims 1,9,11,23,26</p> <p>see page 12; examples 2-5</p> <p>---</p>	1,2,4-6, 8,9,11, 12
X	<p>DATABASE WPI</p> <p>Section Ch, Week 9344</p> <p>Derwent Publications Ltd., London, GB;</p> <p>Class B05, AN 93-348346</p> <p>XP002042144</p> <p>&amp; JP 05 255 080 A (TAISHO PHARM.) , 5</p> <p>October 1993</p> <p>see abstract</p> <p>---</p> <p>-/-</p>	1,2,5,8, 9,11,12

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

30 September 1997

Date of mailing of the international search report

15.10.97

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## INTERNATIONAL SEARCH REPORT

International Application No	PCT/EP 97/01781
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 892 889 A (PAULA S. KIRK, ET AL.) 9 January 1990 see claims 1,4,6,10 see column 4; example 1 -----	1-3,6,8, 9,11,12

**INTERNATIONAL SEARCH REPORT**Int. Appl. No  
PCT/EP 97/01781

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 143576 A	05-06-85	CA 1201383 A AU 3548484 A JP 60123421 A	04-03-86 30-05-85 02-07-85
US 4892889 A	09-01-90	CA 1324576 A	23-11-93

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 97/01781

A. KLASIFIZIERUNG DES ANMELDUNGSGEGENSTANDES  
IPK 6 A61K9/14 A61K9/20 A61K9/00

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IPK 6 A61K

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Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

## C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP 0 143 576 A (WARNER LAMBERT) 5.Juni 1985 siehe Ansprüche 1,9,11,23,26 siehe Seite 12; Beispiele 2-5 ---	1,2,4-6, 8,9,11, 12
X	DATABASE WPI Section Ch, Week 9344 Derwent Publications Ltd., London, GB; Class B05, AN 93-348346 XP002042144 & JP 05 255 080 A (TAISHO PHARM.) , 5.Oktober 1993 siehe Zusammenfassung ---	1,2,5,8, 9,11,12

Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

Siehe Anhang Patentfamilie

\* Besondere Kategorien von angegebenen Veröffentlichungen :

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Bevollmächtigter Bediensteter

Ventura Amat, A

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 97/01781

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US 4 892 889 A (PAULA S. KIRK, ET AL.) 9.Januar 1990 siehe Ansprüche 1,4,6,10 siehe Spalte 4; Beispiel 1 -----	1-3,6,8, 9,11,12

**INTERNATIONALER RECHERCHENBERICHT**

Intern. sales Aktenzeichen

**PCT/EP 97/01781**

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 143576 A	05-06-85	CA 1201383 A AU 3548484 A JP 60123421 A	04-03-86 30-05-85 02-07-85
US 4892889 A	09-01-90	CA 1324576 A	23-11-93